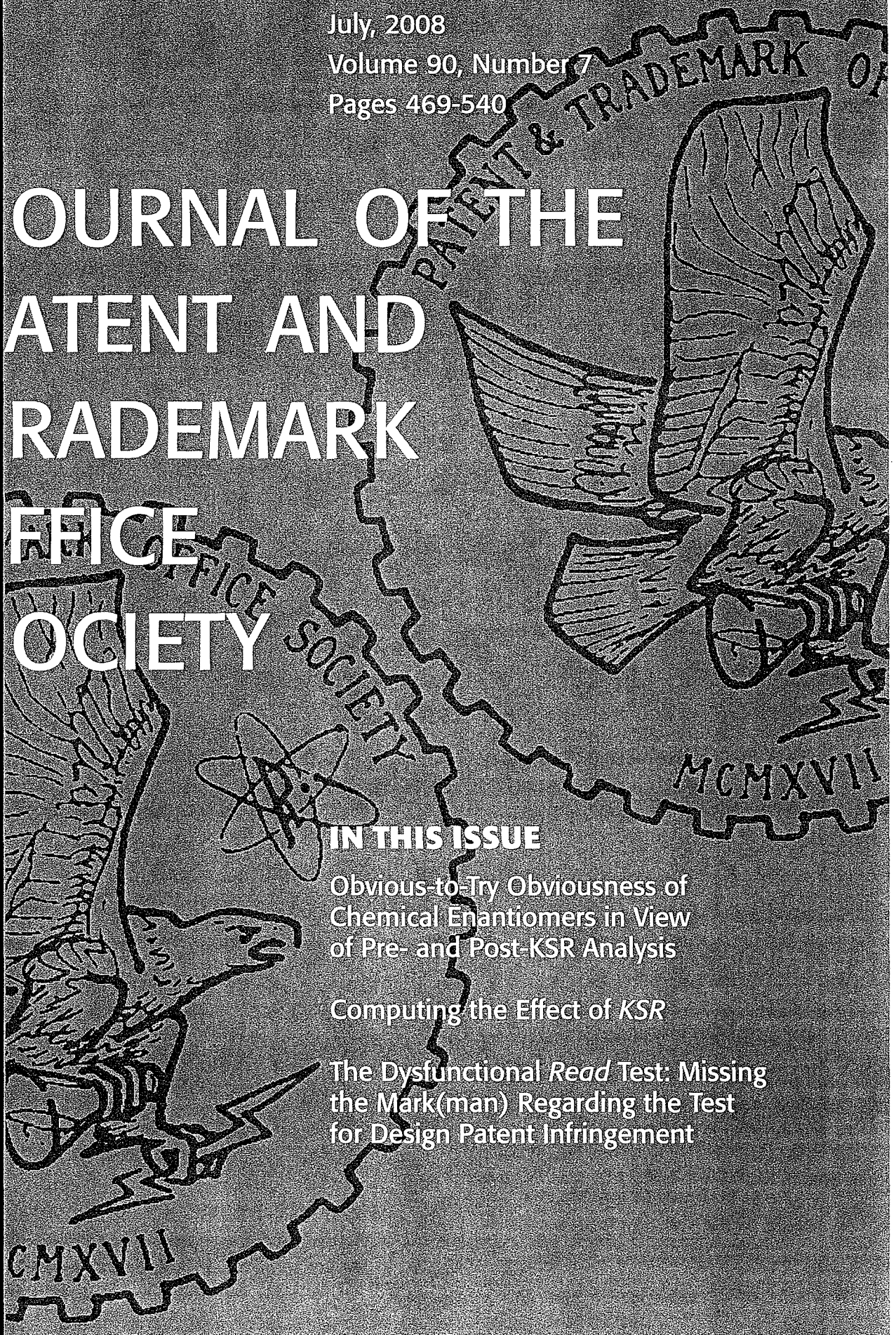
July, 2008
Volume 90, Number 7
Pages 469-540

JOURNAL OF THE PATENT AND TRADEMARK OFFICE SOCIETY



IN THIS ISSUE

Obvious-to-Try Obviousness of Chemical Enantiomers in View of Pre- and Post-*KSR* Analysis

Jonathan M. Spenner*

* Jonathan M. Spenner is a Technical Advisor at Leydig, Voit & Mayer in Chicago. Dr. Spenner is registered to practice before the U.S. Patent and Trademark office, and specializes in the biotechnology, pharmaceuticals, and chemistry fields. Dr. Spenner has experience in the drafting and prosecution of U.S. and international patent applications and has performed freedom-to-operate, patentability, validity, and transactional due diligence analyses, including managing international patent portfolios for both large pharmaceutical companies and small biotechnology companies. Prior to joining Leydig, Voit & Mayer, Dr. Spenner worked at prominent law firms in New York City. Dr. Spenner received his B.A. in biological sciences, *cum laude*, from Northwestern University in 1999 and a Ph.D. in molecular biophysics from The Johns Hopkins University School of Medicine in 2004, where his doctoral dissertation research was in the area of biomacromolecular thermodynamics and structure. Dr. Spenner is currently scheduled to complete his J.D. from Fordham University School of Law in May 2009. He would like to thank Prof. Brian D. Coggio and Prof. John J. Normile, Jr. of Fordham University School of Law for reviewing the manuscript. He would also like to thank Mr. Richard Gervase and Mr. Brian Hopkins for (lively) discussions. As Mr. Gervase pointed out the post-*KSR* world appears to some to be drastically different than as it was pre-*KSR*. However, I hope to show in this paper that no change occurred in the substantive law due to *KSR* and that, if any change did occur, it is only due to a refocusing of attention on the law of obviousness or through the progression of science.

I. Introduction

A. Policy and Importance

The patent laws[1] are designed to keep that which is already in the public domain from being unjustly sequestered and monopolized. The concept of an invention being completely disclosed within a single piece of prior art,[2] and thus being within the public domain and unavailable for patenting, is the concept of anticipation, which is codified at 35 U.S.C. § 102 (2000). Although not described within a single piece of prior art, an invention may still be unpatentable if the invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Title 35, U.S.C. § 103(a) (2000) reads:

> 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 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.

Thus, to determine if an invention is unpatentable as obvious, it is important to determine what a person having ordinary skill in the art knew at the pertinent time and what the requirements are, beyond disclosure of the elements of a given invention (such as in anticipation), to arrive at an invention being deemed obvious. Conversely, it is also important to determine how to potentially overcome an obviousness attack.

Determination of these items, and obviousness in general, is extremely important to the pharmaceutical industry. For the innovators,[3] the obviousness would invalidate patent claims and thus also nullify years of research and millions of dollars in investment. For the generics,[4] a more stringent obviousness test could potentially produce a larger generic presence in the marketplace due to successful Paragraph IV certifications of patent invalidity filed with Abbreviated New Drug Applications ("A. N. D. A.s") under 21 U.S.C. § 355(j)(5)(B)(iii) (2000).[5] A recent article

1 Codified at Title 35 of the United States Code.

2 *See* U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE (8th ed. 2001, incorporating Revision 6, Sept. 2007) (hereinafter "M.P.E.P.") §§ 901, 2121-29 for a discussion of what comprises "prior art." The M.P.E.P. is issued by the U.S. Patent and Trademark Office ("U.S.P.T.O.") to provide examination guidelines to its corps of patent examiners.

3 "Innovator" pharmaceutical companies have research and development ("R&D") programs aimed at the discovery of new drugs for use in treatment.

4 "Generic" pharmaceutical companies do not have their own R&D programs, instead selling drugs developed and tested by innovator companies. Generic companies need only show that a generic drug is bioequivalent to a drug that has already received Food and Drug Administration ("F.D.A.") approval.

5 Generics can file an ANDA claiming that an innovator's patent covering a compound "is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the abbreviated application is submitted. The applicant shall entitle such a certification 'Paragraph IV Certification'." 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

cited worldwide pharmaceutical sales at over half-a-trillion dollars,[6] with chiral drugs approaching $200 billion.[7] Therefore, there is a lot at stake should there be a change in the patent laws regarding obviousness.

The pharmaceutical industry is also very susceptible to claims of obviousness, especially under an "obvious-to-try" rubric. This is due to the nature of the experimentation required to discover, design, and/or develop new active pharmaceutical compounds. As Judge Baldwin described in his dissent in *In re Merck*[8] where a drug was found to be obvious:

> The obvious-to-try analysis is an attack on the method of making an invention that specifically penalizes people in areas of endeavor where advances are won only by great effort and expense. The pharmaceutical field is particularly hard hit because there is an over abundance of structures that are obvious-to-try.[9]

Therefore, the natural progression of science within R&D programs of the pharmaceutical industry involves what some may deem to be obvious-to-try. However, what is the meaning of "obvious-to-try" and how does it fit into an obviousness analysis? What is the state-of-the-law on obvious-to-try obviousness, and how does/will the state-of-the-art affect this determination? Where do enantiomeric drugs lie? These are questions that this paper attempts to answer.

B. Thesis

The Supreme Court case of *KSR International Co. v. Teleflex, Inc.*[10] was very closely watched and has been heralded by some as causing a paradigmatic shift in the law of obviousness.[11] However, a close scrutiny of the case law history shows that *KSR* is more of an anomalous case in which the Supreme Court reminds the Federal Circuit to follow its own precedent and solidifies the "finite" obvious-to-try rationale as permissible in raising a *prima facie* obviousness rejection while rejecting the oft cited "non-finite" obvious-to-try rationale as impermissible ("non-finite" being used by the author to distinguish from "finite"). This paper analyzes the prior case law leading up to *KSR* and the subsequent application of obviousness law after *KSR* in an attempt to show that the law of obviousness has

6 Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 STAN. TECH. L. REV. 2, ¶ 1 (2007) and citations therein. Darrow is an excellent article on the patentability of enantiomers, and is recommended by the author of this paper as important reading. It is also cited throughout this paper. However, Darrow was published prior to *KSR* (Feb. 27, 2007) and thus does not address what affect *KSR* has had on the law of obviousness. Additionally, the development of the parsing of the obvious-to-try standard into the impermissible non-finite obvious-to-try argument and the permissible finite obvious-to-try argument is discussed herein but not within Darrow. This paper also proceeds using more of an in-depth case-by-case analysis and presents how cases subsequent to *KSR* follow the case law developed up to and including *KSR*; Darrow does not present these issues.

7 *Id.* ¶ 2 and citations therein.

8 *In re* Merck & Co., 800 F.2d 1091 (Fed. Cir. 1986) (Baldwin, J., dissenting).

9 *Id.* at 1100.

10 KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007).

11 Brian A. Cocca and Christopher R. Lewis, *A Paradigm Shift in Obviousness for Pharma, Biotech*, IPLAW360, Mar. 3, 2008, http://ip.law360.com/Secure/ViewArticle.aspx?id=48845.

not experienced a *substantive* change.[12] There has only been a rediscovery or refocusing of pre-existing precedent, in which the *practical* effects of this rediscovery/focusing on future patent examinations and litigations may manifest in a slight increase in difficulty in refuting a *prima facie* obviousness argument under section 103(a). This likely would be due mostly to a heightened awareness of the finite obvious-to-try rationale and otherwise through advances in the art.

This paper will show the progression of the law of obviousness using chemical enantiomers both in a general and as an exemplary manner: This paper will follow the progression of obviousness both generally (*i.e.*, development of the obviousness test requirements) and specifically as applied to the case of enantiomers. Based upon this application, the paper will show that the state-of-the-law does not currently presume that enantiomers of a racemate are obvious over the racemate; however, due to the present state-of-the-art, this presumption may likely change.

C. Outline of the Paper

This paper will start by giving background on the chemistry of enantiomers. Background on the law of obviousness then will be given, first by distinguishing between obviousness and *prima facie* obviousness and then moving on to a description of the person of ordinary skill in the art of section 103. The background into the law will continue with development of the obviousness test elements of motivation and reasonable expectation of success. These then will be contrasted with the obviousness-vitiating concept of teaching away. Next, the obvious-to-try argument will be developed, showing that the finite and non-finite obvious-to-try rationales have existed in the law long before *KSR*. Unexpected results will then be discussed, showing what types of results are considered to overcome *prima facie* obviousness. The size of an enantiomer genus will then be discussed. Next, the Federal Circuit's pre-*KSR* flexible application of the teaching, suggestion, motivation test will be described. Relevant cases will be used as particular examples of previously discussed topics and/or to bring together multiple topics and to show how the principles developed prior to *KSR* are being applied after *KSR*.

II. Background: Chemistry

Organic chemical compounds contain carbon atoms covalently bonded to (*i.e.*, connected through the sharing of electrons with) other atoms.[13] Each carbon atom normally has a valence of four, which means that it may form four bonds with one to four other atoms.[14] When a carbon atom has four single bonds with four other atoms,[15] the four other atoms around the carbon atom usually form a tetrahedral spatial arrangement.[16]

12 *See* Lester Horwitz, *Lester Horwitz on Some Strategies on the Question of Obviousness and How the Obviousness Objection Will be Couched*, LexisNexis® Expert Commentaries, Oct. 25, 2007, at 1 (LEXIS); *High Court's Patent Ruling on Obviousness was not Paradigm Shift, Judges Agree*, PATENT, TRADEMARK & COPYRIGHT LAW DAILY (Oct. 10, 2007)

13 L. G. WADE, JR., ORGANIC CHEMISTRY 1 (3d ed. 1995).

14 *Id.* at 9.

15 These other atoms may be single atoms or also themselves covalently bonded to additional atoms.

16 WADE, *supra* note 13, at 48-49.

Isomers are different compounds having identical chemical formula.[17] One type of isomerism is structural isomerism in which the atoms are connected differently.[18] Another type is stereoisomerism in which the atoms are connected to the same atoms; however, the compounds differ in how their atoms are oriented in space.[19] Enantiomers are a subcategory of stereoisomers in which the stereoisomers are nonsuperimposable mirror images of one another.[20] Such enantiomeric compounds are often analogized to a person's left and right hands.[21] Although they are similar, the left hand can not be rotated or translated to be superimposed upon the right hand. The same is true for enantiomers. Enantiomers may contain any number of chiral centers, which may include asymmetric carbons arranged tetrahedrally and connected to four different atoms or groups of atoms.

Molecules that are mirror images of one another, such as enantiomers, individually have nearly identical physical properties.[22] However, separate enantiomers will rotate plane-polarized light[23] in opposite directions, thus giving enantiomers optical activity.[24] The enantiomer that rotates the plane-polarized light to the right (clockwise) is termed the "dextrorotatory" or "*d*-" or "(+)" isomer, and the enantiomer that rotates the plane-polarized light to the left is termed the "levorotatory" or "*l*-" or "(-)" isomer.[25] Enantiomers may also be designated by the absolute configuration of atoms around the stereogenic atom (*i.e.*, a chiral center, an atom

17 *Id.* at 57; Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1295 (Fed. Cir. 2007) ("[A]n isomer of a compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but with those atoms arranged differently."); Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (D.W.Va. 2004), *aff'd*, 161 Fed. Appx. 944 (2005) ("An isomer is one of a number of molecules that have the same chemical formula (the same constituent atoms), but the atoms are arranged in a unique pattern. For example, C4H10 can be arranged as either *n*-butane (all carbons arranged in a chain) or isobutane (three methyl groups arranged around a central carbon atom).").

18 WADE, *supra* note 13, at 57.

19 *Id.*; Aventis, 499 F.3d at 1295 ("A stereoisomer is an isomer in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs."); Forest Labs., Inc. v. Ivax Pharms., Inc., 501 F.3d 1263, 1265 (Fed. Cir. 2007) ("Stereoisomers are compounds that contain the same constituent atoms and the same bonding between those atoms but have different spatial arrangements.").

20 WADE, *supra* note 13, at 177; Forest Labs, 501 F.3d at 1265 ("Enantiomers are stereoisomers that are nonsuperimposable mirror images of one another."); Ortho-McNeil, 348 F. Supp. 2d at 720 ("An enantiomer is one of a pair of isomers that are non-superimposeable mirror images of each other.") (internal footnote omitted).

21 Ortho-McNeil, 348 F. Supp. 2d at 720.

22 WADE, *supra* note 13, at 186.

23 Plane-polarized light is composed of electromagnetic radiation in the visible region in which the electric and magnetic component vectors of the photons oscillate in phase. *E.g.* Ortho-McNeil, 348 F. Supp. 2d at 720 n.5 ("Polarized light is normal light that has been filtered to allow the light to shine only in one direction (normal light shines in all directions).").

24 WADE, *supra* note 13, at 188.

25 *Id.* at 189; Forest Labs, 501 F.3d at 1265 ("Enantiomers accordingly exhibit different optical activity; the enantiomer that rotates a plane of polarized light in the clockwise direction is the (+)-enantiomer; the enantiomer that rotates a plane of polarized light in the counterclockwise direction is the (-)-enantiomer. "); Ortho-McNeil, 348 F. Supp. 2d at 720-21 ("The right/left nomenclature also stems from the fact that enantiomers are inherently 'optically active.' That is, an enantiomer will rotate a plane of polarized light clockwise (dextrorotatory) or counterclockwise (levorotatory). Moreover, a given pair of enantiomers will always rotate polarized light in equal and opposite directions. For example, if the dextrorotatory enantiomer rotates polarized light 90° to the right (clockwise), then the levorotatory enantiomer will rotate the polarized light 90° to the left (counterclockwise). Because enantiomers have identical chemical formulae, chemists distinguish between the chemical names of enantiomeric pairs by preceding each with a symbol that reflects the direction the enantiomer rotates polarized light: '(+)' for dextrorotatory enantiomers, and '(-)' for levorotatory enantiomers.") (internal footnote omitted).

which gives a stereoisomer its stereoisomerism) as the *R* or *S* isomer.[26] The relationship of *d-/l-* to *R/S* must be empirically determined since the direction of plane-polarized light rotation can not be determined based on the *R/S* configuration, and *vice versa*.[27]

Although enantiomers have nearly identical physical properties, they often have very different biological activities.[28] This is due to the chirality of biological molecules, such as proteins, and the resulting affect on, *e.g.*, enzyme active sites. Whereas an enzyme may recognize and catalyze a reaction with one enantiomer due to physical and chemical complementarity with the enzyme's active site, the same enzyme may not recognize the other enantiomer due to noncomplementarity.[29] However, *in vivo*, one enantiomer may be converted to the other enantiomer through the process of racemization. "Racemization is a process whereby a compound consisting of a single enantiomer is converted to a one-to-one mixture of that enantiomer and its opposite (*i.e.*, the racemate) by the cleavage and reformation of a chemical bond at the chiral center of the molecule."[30] Thus, one enantiomer may be bioequivalent to another, depending on whether racemization occurs in the body.

Racemates[31] are mixtures of equal amounts of enantiomers[32] and are denoted as (*d,l*) or (+/-) pairs for the stereoisomerism of a given chiral center.[33] A racemate exhibits no net rotation of plane-polarized light and is thus optically inactive.[34] A racemate may exhibit properties (other than optical activity) that are different from the separate enantiomers.[35] Finally, in the laboratory, in the absence of asymmetric synthesis, synthesis of one enantiomer will necessarily produce all other enantiomers.[36]

Since there are two enantiomers in a racemate of a compound with a single chiral center, a racemate potentially comprises a very small genus of two species.[37] As the number of chiral centers increases, the

26 WADE, *supra* note 13, at 188; Forest Labs, 501 F.3d at 1265 ("Enantiomers may also be designated as the *S*-enantiomer and the *R*-enantiomer according to a different criterion relating to the location of the chiral centers.").

27 WADE, *supra* note 13, at 188; Ortho-McNeil, 348 F. Supp. 2d at 721 ("Chemists also distinguish between enantiomers by designating an enantiomer as either 'R' or 'S' based upon the arrangement of certain atoms at the enantiomer's 'chiral center.' Where one enantiomer is an 'R,' the other will be an 'S.'") (internal footnote omitted).

28 Darrow, *supra* note 6, ¶ 7 and citations therein.

29 *See id.*

30 Sanofi-Synthelabo v. Apotex, Inc., 492 F. Supp. 2d 353, 369 (S.D.N.Y. 2007).

31 It is noted that Darrow, *supra* note 6, ¶ 9 n.35 states that racemates are often termed "racemic mixtures" and that this terminology is incorrect. Therefore, the term "racemate" will be used throughout this paper, unless "racemic mixture" is given in a direct quote.

32 WADE, *supra* note 13, at 195; Forest Labs, 501 F.3d at 1265-66; Ortho-McNeil, 348 F. Supp. 2d at 721.

33 WADE, *supra* note 13, at 195; Ortho-McNeil, 348 F. Supp. 2d at 721 ("Chemists also have a specific nomenclature for racemic compounds - the chemical name is preceded by either '(+/-)' or 'RS' (or both).").

34 WADE, *supra* note 13, at 195; Ortho-McNeil, 348 F. Supp. 2d at 721 ("A racemic compound is optically inactive because, for every dextrorotatory enantiomer rotating polarized light to the right, there exists a levorotatory enantiomer rotating light to the left, resulting in a net rotation of zero.").

35 *In re* Adamson, 275 F.2d 952, 953 (C.C.P.A. 1960) ("[T]he chemical and physical properties of a racemate may be substantially different that [*sic*] those of its stereo-isomers."), citing KARRER, ORGANIC CHEMISTRY 92-102 (2d ed. 1946).

36 WADE, *supra* note 13, at 195; Darrow, *supra* note 6, ¶ 9; Ortho-McNeil, 348 F. Supp. 2d at 721 ("When chemists first find or synthesize a given enantiomeric pair, the enantiomers always occur in a perfect 1:1 ratio.").

37 Darrow, *supra* note 6, ¶ 28.

number of species within a racemate also increases;[38] and this increase would be 2^n, where n is the number of chiral centers. However, for small molecule pharmaceuticals, the genus of compounds will necessarily include a relatively small number of species. Also, the F.D.A. has issued a policy in which testing of single enantiomers is required during the drug approval process whenever a drug is a racemate.[39] The number of enantiomers and the incentive to isolate single enantiomers will play a role in determining whether enantiomers are ultimately obvious.

As is described by Darrow[40] and Coggio and Hird,[41] the question of obviousness directed to enantiomers is usually not whether one enantiomer is obvious over another enantiomer but whether an isolated enantiomer is obvious over its racemate. Therefore, a question becomes whether it is obvious-to-try to separate and isolate enantiomers from a given racemate. Furthermore, does knowledge of the chemical structure of an enantiomer alone give rise to *prima facie* obviousness? These are further questions that this paper will attempt to answer.

III. Background: Law of Obviousness before KSR

A. Obviousness and Prima Facie Obviousness

The elements of the obviousness test and the means to rebut it are described in detail in this paper. However, as Darrow[42] and the M.P.E.P.[43] point out, obviousness needs to be distinguished from *prima facie* obviousness. Darrow states:

> *Prima facie* obviousness is a procedural tool, used to shift the burden of proof to the applicant. That is, once a showing of *prima facie* obviousness is made, the applicant then has the opportunity to rebut (and bears the burden of rebutting) this *prima facie* showing. Therefore, even if a court determines that an enantiomer is *prima facie* obvious over its racemate, it may still be nonobvious and therefore patentable if the presumption of obviousness can be overcome.[44]

Therefore, fulfillment of the obviousness test elements creates a *prima facie* obviousness situation unless and until the patent applicant makes a showing sufficient to overcome the argument. The M.P.E.P. continues by stating that the examiner is charged with the burden of proving a *prima facie* obvious case. If the examiner can not, then there is no need for the applicant to proffer any evidence to demonstrate an invention's nonobviousness.[45]

B. A Person of Ordinary Skill in the Art

The concept of motivation only has meaning when attached to the person with whom the motivation would have an

38 *Id.*

39 Darrow, *supra* note 6, ¶ 9 and citations therein.

40 *Id.*

41 Brian D. Coggio & Steven N. Hird, *The Patentability of Drug Enantiomers: Two Recent Decisions Affect Whether an Individual Enantiomer is patentable over a Racemate,* NEW JERSEY L. J. (Oct. 1, 2007).

42 Darrow, *supra* note 6, ¶¶ 43-45.

43 M.P.E.P. at § 2142 and cases cited therein.

44 Darrow, *supra* note 6, ¶ 44 and citations therein.

45 M.P.E.P. at § 2142.

effect. This is the proverbial person of ordinary skill in the art, or "POSITA." If an invention would have been obvious to a POSITA prior to the making of a patent application, as stated by § 103, then the invention is unpatentable. Therefore, what are the characteristics of a POSITA?

In brief, a POSITA is a hypothetical person[46] and has the level of skill as determined within the art in general, which does not specifically consider the level of skill of the inventors.[47] The M.P.E.P. describes factors that may be used to determine the level of ordinary skill in the art:

> Factors that may be considered in determining the level of ordinary skill in the art may include: (A) type of problems encountered in the art; (B) prior art solutions to those problems; (C) rapidity with which innovations are made; (D) sophistication of the technology; and (E) educational level of active workers in the field. In a given case, every factor may not be present, and one or more factors may predominate.[48]

Additionally, it is only what would be objectively obvious to the POSITA that would potentially make an invention obvious.[49] Furthermore, the Supreme Court in *KSR* stated, "A person of ordinary skill is also a person of ordinary creativity, not an automaton."[50] As knowledge of enantiomers increases and to separate them techniques improve as the state-of-the-art progresses, less innovation and less creativity will be needed to isolate enantiomers from their racemates; therefore, the enantiomers will more likely be obvious over a prior art racemate.[51]

C. Motivation

1. Court of Customs and Patent Appeals

The groundwork for analyzing whether an enantiomer is obvious over a racemate starts with *In re Williams*.[52] There, the patent applicant claimed the laevo rotary form (*i.e.*, the *l*-isomer) of a compound as substantially free from the dextro rotary isomer (*i.e.*, the *d*-isomer) of a racemic pair.[53] The examiner rejected the claim as lacking invention over the prior art, which discloses the claimed compound.[54] The Board of Appeals of the U.S.P.T.O. upheld the rejection.[55] Both the examiner and the Board argued that the disclosure

46 Std. Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985).

47 Stewart-Warner Corp. v. Pontiac, 767 F.2d 1563, 1570 (Fed. Cir. 1985).

48 M.P.E.P. at § 2141.03, citing In re GPAC, 57 F.3d 1573, 1579 (Fed. Cir. 1995), Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc., 807 F.2d 955, 962 (Fed. Cir. 1986), and Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 696 (Fed. Cir. 1983) (quotation marks omitted).

49 Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 718 (Fed. Cir. 1991), citing Kloster Speedsteel AB v. Crucible, Inc., 793 F.2d 1565, 1574 (Fed. Cir. 1986), cert. denied, 479 U.S. 1034 (1987).

50 KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007).

51 *See* Darrow, *supra* note 6, ¶ 16.

52 *In re* Williams, 171 F.2d 319 (C.C.P.A. 1948).

53 *Id.* at 319.

54 *Id.* at 320. Note that *Williams* was decided prior to the enactment of the 1952 Patent Act, which first codified 35 U.S.C. § 103 and the "obviousness" language. Therefore, the court refers to claims of a patent as lacking invention if those claims are what are now would be considered obvious over the prior art.

55 *Id.*

of the compound necessarily discloses the *l*- and *d*-isomers of the compound, and that separation of the *l*- and *d*-isomers was known in the art.[56] However, the Court of Customs and Patent Appeals ("C.C.P.A.")[57] found that the prior art does not show that the compound is racemic, and the compound was not actually shown to be racemic.[58] The court continued by stating the evidence relied upon by the examiner and Board, which shows that the compound is racemic, post-dates the filing date of the patent application.[59] Thus, it would not have been known at the time the application was filed that the compound exists as a racemic pair; therefore, it would not have been obvious for one of skill[60] in the art to resolve the racemate into its enantiomeric components.[61] In *Williams*, the court stated that there was no knowledge that the claimed compound is racemic and thus exists as an enantiomeric pair, and no *prior* art evidence was presented to indicate this.

In *In re Adamson*,[62] a prior art reference was cited by the U.S.P.T.O. to establish a compound as racemic. There, the claims were directed to the *l*-isomers of two compounds and salts thereof substantially separated from the *d*-isomers.[63] The C.C.P.A. found that prior art references disclose the compounds but not whether the compounds are racemic or that the *d*- or *l*-isomers exist.[64] However, the court also found that another prior art reference describes stereoisomerism,[65] methods of resolving the stereoisomers (including the method used by the applicants),[66] and discloses the fact that "[S]ynthetically produced organic compounds containing an asymmetric carbon atom are racemic, *i.e.*, optically inactive mixtures of equal amounts of the dextro- and laevo-isomers."[67] Thus, during the normal (*i.e.*, not asymmetric) synthesis of a compound that has a stereogenic center, a racemate would have been known to form; and this racemate contains equal amounts of the *d*- and *l*-isomers. Therefore, it would have been obvious for one of ordinary skill in the art to recognize that the claimed compounds as disclosed are racemic, even though the prior art references disclosing the compounds do not themselves disclose this fact.

56 *Id.*

57 The C.C.P.A. was the predecessor court of the Court of Appeals for the Federal Circuit, founded in 1982.

58 *Williams*, 171 F.2d at 320.

59 *Id.* Note how that, even though the compound was later shown to be racemic and the disclosure of the prior art inherently disclosed both isomers of the enantiomeric pair, the prior art is not considered by the Court here to have provided knowledge of the pair at the time of filing the application. This also will be seen where there would have been no motivation to one of skill in the art to separate the pair since it was not known to be a mixture of isomers.

60 It is noted that the court uses the phrase "one skilled in the art" instead of "one of ordinary skill in the art." 35 U.S.C. § 103 presents the language of "ordinary skill." *See supra.*

61 *Williams*, 171 F.2d at 320.

62 *In re* Adamson, 275 F.2d 952 (C.C.P.A. 1960).

63 *Id.* at 952.

64 *Id.* at 953.

65 *Id.*

66 *Id.*

67 *Id.* at 954.

The applicants attempted to show that the claimed compounds would have been nonobvious due to an unexpectedly greater biological activity of the *l*-isomer over the *d*-isomer and racemate.[68] However, the Board of Appeals of the U.S.P.T.O. found that the results were not persuasive.[69] The court agreed, stating that there was no reason of record to believe that there would not be a difference in activities among separated isomers compared to the racemate.[70] Furthermore, the court noted that the toxicity of the racemate lies between that of its isomers, a fact that "appears to [the court] to be particularly expected."[71] Therefore, the results as demonstrated by the applicants did not outweigh the strength of the *prima facie* obvious case presented by the U.S.P.T.O.

At this point, it would appear that enantiomers would be doomed to be at least *prima facie* obvious over their racemates given the type of art found in *Adamson*. However, the applicants there did not present persuasive evidence showing the nonobviousness of the claimed compounds. Also, the *Adamson* court noted that a particular method disclosed by the prior art to separate components of a racemate was used by the applicant to separate the claimed compounds. Thus, the method by which enantiomers are separated also plays a role in the ultimate obviousness determination.

In *Williams*, there would have been no motivation for one of ordinary skill in the art to resolve a compound when it would not have been appreciated that resolution of separate species would have been possible. In *Adamson*, the prior art disclosure that a normal synthesis of a compound with a stereogenic center produces a racemate precluded patentability of the claimed compounds because the existence of separate enantiomeric species would have been recognized in the art, providing the motivation that *Williams* lacked.

The concept of motivation is further developed in *In re Bergel*.[72] Here, a first prior art reference, Harper *et al.*, discloses a non-chlorinated analog of the claimed compound and its *l*-isomer.[73] A second prior art reference, Everett *et al.*, discloses a large genus of chlorinated compounds, similar to the claimed compounds, and includes a general statement that *many* of the compounds in the genus have an inhibiting effect on the growth of certain tumors.[74] However, the C.C.P.A found that Everett *et al.* did not indicate that all or even most of the compounds had the generally stated property.[75] Also, the court found that, since the compounds of Harper *et al.* were not disclosed as having any anti-tumor activity, there would have been no suggestion that such compounds should be modified through chlorination according to Everett *et al.* to produce a tumor growth-inhibiting compound.[76]

68 *Id.* at 954-55.

69 *Id.* at 954.

70 *Id.* at 955.

71 *Id.*

72 *In re* Bergel, 292 F.2d 955 (C.C.P.A. 1961).

73 *Id.* at 956.

74 *Id.*

75 *Id.*

76 *Id.*

Indeed, the Harper *et al.* compounds were only disclosed as being a "metabolic antagonist for the bacillus *enconostoc mesenteroides*[.]"[77] Thus, the claimed compounds were found to be nonobvious over the cited prior art.

A few statements may be made about *Bergel*. It appears that even though some ("many") within a group are described as containing a property, this does not indicate that that property is found in *all* members of the described group. Thus, this may be regarded as an "incomplete" motivation in that the prior art still left doubt whether other compounds in the genus exhibit the same property, especially with the genus being large. The genus for a given enantiomer is usually small, and it is currently known that one enantiomer usually possesses superior properties to the racemate, as discussed *supra*.

Continuing with the progression of the law, the court in *In re Papesch*,[78] citing *In re Lambooy*,[79] stated that it would be obvious to a chemist that compounds may be modified, *e.g.*, by adding a methyl group to various positions of a known compound.[80] However, there is a motivational problem in that a chemist knows this to be true for all compounds and the *reason* for adding a methyl group may not be obvious.[81] In the racemic situation, the act of resolving the enantiomers would be known to a person of ordinary skill in the art, but there would be no motivation for doing so simply because resolution is possible, and more is needed. However, as stated *supra*, that motivation may currently come in the form of a desire to find an enantiomer with more desirable properties than the racemate, *e.g.*, due to F.D.A. policy.

The pertinent facts to analyze in determining whether a claimed invention is obvious over the prior art was set forth by the Supreme court in the landmark case of *Graham v. John Deere Co.*[82] The *Graham* decision provides the factual inquires necessary to sustain the legal determination of obviousness:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.[83]

Furthermore, should inquiry into the above factors indicate that the subject matter of the claims would have been obvious (*i.e.*, *prima facie* obvious), this determination may be rebutted. "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy."[84] Thus, what at a first *prospec-*

77 *Id.*

78 *In re* Papesch, 315 F.2d 381 (C.C.P.A. 1963).

79 *In re* Lambooy, 300 F.2d 950 (C.C.P.A. 1962)

80 *In re* Papesch, 315 F.2d at 390.

81 *Id.*

82 Graham v. John Deere Co., 383 U.S. 1 (1966).

83 *Id.* at 17.

84 *Id.* at 17-18

tive glance appears to have been obvious can actually be *retrospectively* shown to have been nonobvious. This also may be true if unexpected results are shown.

In *In re Stemniski*,[85] the C.C.P.A. held that "close structural similarity alone is not sufficient to create a *prima facie* case of obviousness when the reference compounds lack utility, and thus there is no motivation to make related compounds."[86] Thus, the analysis could turn on whether the compounds are known to have any utility. For racemic drugs, this is mostly inapplicable in that the motivation to resolve the racemate is likely to find an enantiomer with, *e.g.*, greater activity or lower toxicity.

In *In re Wilder*,[87] the C.C.P.A. stated, "[O]ne who claims a compound, *per se*, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties."[88] Enantiomers are structurally similar to the other enantiomers within their racemates. Thus, it would be presumed that the individual enantiomers have similar properties to the racemate.

2. Court of Appeals for the Federal Circuit

Continuing with the progression of the law, the Court of Appeals for the Federal Circuit ("C. A. F. C." or "Federal Circuit") in *In re Grabiak*[89] held: "When chemical compounds have 'very close' structural similarities and similar utilities, without more a *prima facie* case may be made[,]"[90] but also stated that "[W]e have concluded that generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other."[91] The court continued by stating adequate support must be found in the prior art, in this case, for a change in chemical structure.[92] Thus, there must have been a motivation for making the change.

For enantiomers, this concept of change may be extended to the principle that there must have been a motivation in the art to resolve enantiomers from the racemate, thus "changing" the racemate. As discussed *supra*, this motivation may be to find the enantiomer with more desirable properties. However, the method of separation itself will also play a role in determining whether the enantiomers, after resolution, would have been obvious, regardless of the existence of any similar properties or the motivation to separate the enantiomers.

In *In re Dillon*,[93] Dillon claimed tetra-orthoester compounds, which she showed could be used as additives to fuel to reduce particulate emissions. However, the prior art was shown to disclose tri-orthoester compounds, which were known to de-water fuel, and tetra-

85 *In re* Stemniski, 444 F.2d 581 (C.C.P.A. 1971).

86 M.P.E.P. at § 2144.08 II(A)(4)(d).

87 *In re* Wilder, 563 F.2d 457 (C.C.P.A. 1977).

88 *Id.* at 460 (citation omitted).

89 *In re* Grabiak, 769 F.2d 729.

90 *Id.* at 731 (citations omitted).

91 *Id.*; *see also In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995), discussed *infra* (holding although structural similarity may suggest homologs or isomers, etc., the method of preparation may factor into the obviousness analysis).

92 *In re* Grabiak, 769 F.2d at 731-32.

93 *In re* Dillon, 919 F.2d 688 (Fed. Cir. 1990).

orthoesters, which were known to de-water hydraulic fluids.[94] The U.S.P.T.O. and the Federal Circuit found that it would have been obvious to obtain a mixture of fuel and tetra-orthoesters for the purpose of de-watering fuel, based on the prior art, and that Dillon's showing of a new property/consequence of the addition of tetra-orthoesters to fuel, *i.e.*, reduction of particulate emissions, was of no moment.[95] Thus, here, a motivation was found, as required by *Grabiak*, in the prior art to make the claimed change (*i.e.*, add tetra-orthoesters to fuel, instead of just adding tri-orthoesters to fuel, for de-watering the fuel and as a consequence obtain reduced particulate emissions).

3. Summary

Structurally similar compounds, such as enantiomers as compared to their racemates, are presumed to have similar properties. Thus, a showing of dissimilar properties would weigh toward nonobviousness. Motivation must exist for any modification, and the prior art must suggest this modification, *e.g.*, any reason one of ordinary skill in the art would want to resolve a racemate. Motivation for this modification of the racemate is likely to exist as finding an enantiomer with more desirable properties than the racemate. However, even though separation of enantiomers in general may be known, particular enantiomers may not be obvious since the obviousness of the resolution method itself may play a role in determining obviousness.

D. Reasonable Expectation of Success

For a POSITA to have considered an invention obvious, the invention need not be completely predicted by the state-of-the-art. In *In re O'Farrell*,[96] the Federal Circuit states, "Obviousness does not require absolute predictability of success[,]"[97] and "[A]ll that is required is a reasonable expectation of success."[98] Thus, in addition to motivation, a person of ordinary skill in the art needs to have had a reasonable expectation of success in making the invention. For enantiomers, this expectation includes the resolution of the racemate. "[T]he presence–or absence–of a suitably operative, obvious process for making a composition of matter may have an ultimate bearing on whether that composition is obvious–or nonobvious–under 35 U.S.C. 103."[99] Thus, the question to ask is whether the process is nonobvious over prior art processes, not whether the separation was difficult. Furthermore,

> [I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious,

94 *Id.* at 691.

95 *Id.* at 692-93.

96 *In re* O'Farrell, 853 F.2d 894 (Fed. Cir. 1988).

97 *Id.* at 903.

98 *Id.*, citing *In re* Merck & Co., 800 F.2d 1091, 1098 (Fed. Cir. 1986); Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1461 (Fed. Cir. 1984); *In re* Papesch, 315 F.2d 381, 386-87 (C.C.P.A. 1963).

99 *In re* Maloney, 411 F.2d 1321, 1323 (C.C.P.A. 1969) (citations omitted).

> based on the close relationships between their structures and those of prior art compounds.[100]

In *In re Deuel*[101] the Federal Circuit found that although a compound may suggest structurally similar compounds, the production of those similar compounds may not be suggested (and thus not in itself give a motivation to produce them or alternatively not provide a reasonable expectation of success in obtaining them).

> Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties. Similarly, a known compound may suggest its analogs or isomers, either geometric isomers (*cis v. trans*) or position isomers (*e.g.*, ortho *v.* para).[102]

Furthermore, the Federal Circuit then stated that the method of producing the structurally similar compounds must also be considered in any patentability determination.

> The fact that one can conceive a general process in advance for preparing an undefined compound does not mean that a claimed specific compound was precisely envisioned and therefore obvious. A substance may indeed be defined by its process of preparation. That occurs, however, when it has already been prepared by that process and one therefore knows that the result of that process is the stated compound. The process is part of the definition of the compound. But that is not possible in advance, especially when the hypothetical process is only a general one.[103]

Therefore, in terms of enantiomers, the resolution of the racemate will have to be factored into the calculus of whether the enantiomers themselves are obvious over the racemate. Thus, the more difficult and nonobvious the separation, the more likely the enantiomers are nonobvious over the racemate.

The post-*KSR* case of *Takeda v. Alphapharm*[104] contains an excerpt that helps to summarize the Federal Circuit's position.

> [This court] elaborated on this requirement [of *prima facie* obviousness of structurally similar compounds] in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995), where we stated that "[n]ormally a *prima facie* case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide

100 *In re* Hoeksema, 399 F.2d 269, 275 (C.C.P.A. 1968) (internal footnote omitted).

101 *In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995).

102 *Id.* at 1558.

103 *Id.* at 1559-60.

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

> the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, 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. *Id.*[105]

Thus, the method of resolution plays a role in the obviousness analysis. As uncertainty in the art increases, predictability decreases -- as well as any reasonable expectation of successful resolution of a racemate. If the resolution is nonobvious, there would be no reasonable expectation of successfully obtaining the individual enantiomers. Therefore, along with motivation, a reasonable expectation of success is required when changing what is known in the prior art in order to arrive at the claimed invention.

E. Teaching Away

A teaching away may eliminate any motivation or reasonable expectation of success. In *KSR*, the Supreme Court, citing *United States v. Adams*,[106] stated: "The Court relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious."[107] Thus, should the prior art be found to teach away sufficiently from arriving at the claimed invention, a *prima facie* obvious case may not be made.

In order to teach away, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed[.]"[108] Therefore, the teaching away must in some way give a direction in which the art should progress. This direction may be through criticizing or discrediting one method in favor of another. Such a teaching away is even more damaging to a *prima facie* obviousness argument than "incomplete" motivation as was found in *Bergel*, discussed *supra*. Indeed, in the post-*KSR Takeda* case, the Federal Circuit found that a teaching away that the claimed compound would cause "considerable increases in body weight and brown fat weight" was critical in finding the claimed compounds nonobvious, even if the facts otherwise presented a (finite) obvious-to-try situation.[109]

F. Obvious-to-try and Unexpected Results

The impermissible obvious-to-try subcategory of obviousness has been an often used argument in an attempt to rebut an examiner's finding of *prima facie* obvious-

105 *Id.* at 1356, citing *In re* Jones, 958 F.2d 347 (Fed. Cir. 1992); *In re* Dillon, 919 F.2d 688; *In re* Grabiak, 769 F.2d 729; *In re* Lalu, 747 F.2d 703 (Fed. Cir. 1984).

106 United States v. Adams, 383 U.S. 39, 51-52 (1966).

107 KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007).

108 *In re* Fulton, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

109 *See* Takeda Chem. Indus., 492 F.3d at 1358-60.

ness. However, *KSR* states that an obvious-to-try rationale may be used in finding an invention obvious. It is the position of this paper that the obvious-to-try situation, even prior to *KSR*, could always itself be separated into two subcategories, a permissible "finite" obvious-to-try argument and an impermissible "non-finite" obvious-to-try argument. Additionally, if an invention is found to be obvious, even under the finite obvious-to-try rationale, this finding may be rebutted by a sufficient showing of unexpected results or secondary considerations.[110] In *In re Papesch*,[111] the C.C.P.A. stated, "If that which appears, at first blush, to be obvious though new is shown by evidence not to be obvious, then the evidence prevails over surmise or unsupported contention and a rejection based on obviousness must fall."[112] Therefore, unexpected results can be used to show *retrospectively* that an invention would have been nonobvious even though it would have been considered obvious by a POSITA *prospectively* without the benefit of knowing the unexpected results.

1. Obvious-to-try

Prior to any showing of unexpected results, *prima facie* obviousness must be shown. Revisiting *Bergel*, there was a large group of compounds from which to start, where it was possible, through trial-and-error chlorination of the compounds, to find some compounds having antitumor activity. However, the court rejects this since there would have been no motivation here to do so. "[The disclosure of the Everett *et al.* genus] therefore, cannot properly be taken as a suggestion to prepare and test every conceivable compound of the group."[113] Thus appears a "non-finite" obvious-to-try scenario where there are a potentially infinite or otherwise large group of compounds from which to start.

In re Merck[114] shows *prima facie* obviousness grounded in a "finite" obvious-to-try situation, unlike the non-finite situation of *Bergel*. Whereas the *Lambooy* case[115] involved the addition of atoms to known compounds, *In re Merck* involved replacement of isosteric atoms[116] in known compounds. The compound claimed in the method of use claims differs from a prior art compound only in that it has an unsaturated carbon atom replaced with a nitrogen atom.[117] The Federal Circuit found the compound to be obvious over the prior art in that the prior art taught bioisosteric replacement, which was commonly used, and specifically taught replacement of unsaturated carbons with nitrogens.[118] Further, the court found that this technique would

110 This paper will focus on rebuttal using unexpected results.

111 *In re* Papesch, 315 F.2d 381 (C.C.P.A. 1963).

112 *Id.* at 386-87.

113 *In re* Bergel, 292 F.2d at 956.

114 *In re* Merck & Co., 800 F.2d 1091 (Fed. Cir. 1986).

115 *In re* Lambooy, 300 F.2d 950 (C.C.P.A. 1962).

116 Isosteric atoms were defined by the prior art "as atoms, ions or molecules in which the peripheral layers of electrons can be considered identical." *In re* Merck, 800 F.2d at 1094.

117 *Id.*

118 *Id.* at 1096-97.

have been within the grasp of the POSITA who would have expected similar results for the claimed compound.[119]

The applicant stated that the U.S.P.T.O. used an impermissible obvious-to-try standard, and that there would have been no motivation in the prior art to arrive at the claimed invention.[120] However, the court stated that (1) the claimed compound and the prior art compounds are closely structurally related, (2) both were known as psychotropic drugs, (3) the similar structures (claimed and in the prior art) would behave similarly as suggested by the prior art, (4) absolute predictability is not required, and (5) only a reasonable expectation of success is necessary.[121] The court stated that the properties of the claimed compound were not unexpected because the degree of more potent sedative and stronger anticholinergic effects would not have been unexpected.[122] Also, the court agreed with the position of the U.S.P.T.O. that a slight modification would produce some difference in activity,[123] a situation similar to *Adamson*. This is in accord with the principle that similar compounds are expected to have similar (*i.e.*, not necessarily identical) properties.

Thus, if anything, this would represent a finite obvious-to-try situation. There was a compound known in the prior art that possesses certain beneficial properties. Thus, the starting point for the POSITA would have been a finite number of possibilities (here, a single compound). Through the use of a well-known technique (isosterism/bioisosterism), which was within the grasp of the POSITA, it would have been contemplated to modify the compound in the way applicants did to arrive at the invention. The motivation existed in the art to produce similar properties in an attempt to improve those properties, and there was a reasonable expectation of success in making the modification based on the prior art description of the technique. The properties of the new compound exhibit properties similar to those of the prior art compound, and no new and significant property was shown.

The obvious-to-try standard is discussed at length in *In re O'Farrell*.[124] The Federal Circuit stated that the meaning of obvious-to-try is sometimes lost and gives two reasons when obvious-to-try has been improperly used:

> It is true that this court and its predecessors have repeatedly emphasized that "obvious-to-try" is not the standard under § 103. However, the meaning of this maxim is sometimes lost. Any invention that would in fact have been obvious under § 103 would also have been, in a sense, obvious-to-try. The question is: when is an invention that was obvious-to-try nevertheless nonobvious?
>
> The admonition that "obvious-to-try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious-to-try" would

119 *Id.* at 1097.

120 *Id.*

121 *Id.* (citations omitted).

122 *Id.* at 1098-99.

123 *Id.* at 1099.

124 *In re* O'Farrell, 853 F.2d 894 (Fed. Cir. 1988).

> have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious-to-try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.[125]

The court found that neither situation applied in *O'Farrell*.[126]

Therefore, an impermissible obvious-to-try argument would be predicated on a situation where no guidance or only general guidance is in the prior art and within the knowledge of the POSITA. An example of such a situation is where there are an infinite number of starting points, *e.g.*, variation of potentially an infinite number of parameters in a potentially infinite number of ways or combinations.[127] In *Bergel*, the claimed modification would have required trial-and-error chlorination of a large genus to arrive at the invention. This is an example of a non-finite obvious-to-try situation. According to *O'Farrell*, trial-and-error is not a (finite) obvious-to-try situation. In contrast, in *In re Merck*, the starting point was readily envisaged, and the method to make the change to make the compound was within the grasp of the POSITA, yielding expected results. *In re Merck* is an example of the finite obvious-to-try situation.

Finite obvious-to-try also was seen in *Merck v. Biocraft*[128] where Merck's combination drug was found to be obvious over the prior art. The district court found that the combination of two drugs within a formulation would merely have been obvious-to-try and thus not obvious under section 103.[129] The Federal Circuit reversed as a matter of law.[130] The court cited *O'Farrell* as stating that obvious-to-try is where the prior art gives no indication of which parameters are critical or no direction regarding which of many possible choices would likely be successful (*i.e.*, what the author of this paper terms impermissible non-finite obvious-to-try).[131] The court found motivation in the art to co-administer the drugs in the claimed combination, even though there were a possible 1200 combinations disclosed[132]: "That the '813 patent discloses a multitude of effective combinations does not render any particular formulation less obvious."[133] Furthermore, in determining obviousness, the court found that "the fact that a specif-

125 *Id.* at 903 (citations omitted).

126 *Id.*

127 It is noted that even without an infinite number of starting points, a situation may arise where an invention is not obvious over the prior art, *e.g.*, such as when the method to arrive at the invention is itself nonobvious, as in the case for the resolution of some enantiomers. *See supra.*

128 Merck & Co. v. Biocraft Laboratories, Inc., 874 F.2d 804 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

129 *Id.* at 807.

130 *Id.*

131 *Id.*, citing *In re* O'Farrell, 853 F.2d at 903.

132 Merck & Co., 874 F.2d at 807.

133 *Id.*

ic [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred [*sic*] embodiments, must be considered."[134] Merck also failed to show unexpected results since the combination of the two drugs, each causing sodium excretion, would expectedly cause an increase in sodium excretion over either one drug used alone.[135] Furthermore, the court found that development of the dosages was routine.[136] Although "Patentability shall not be negatived by the manner in which the invention was made"[137] as required by section 103, the court stated, "[T]he converse is equally true: patentability is not imparted where 'the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.'"[138] Secondary considerations were not found to be persuasive.[139]

2. Unexpected Results

a. Court of Customs and Patent Appeals

Revisiting the *Adamson* case, the experimental results presented by the applicant were not found to be "unexpected" to rebut the finding of *prima facie* obviousness. There, the record showed:

> the laevo-isomer to be about twice as active as the racemate, and the dextro-isomer to be virtually inactive, as antispasmodics. Karrer [a prior art reference] teaches that the pharmacological activity of two stereo-isomers may differ substantially because of the nature of the substances with which they react to produce their physiological effects.[140]

The C.C.P.A. continued by stating that in experimentally establishing the optical isomers, racemates, and certain salts thereof described by the applicant/appellants have different spasmolytic biological activities,

> [A]ppellants have done no more than is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art, *i.e.*, the activities are different. The toxicity of the racemate is shown by the affidavit to lie between that of its isomers, which fact appears to us to be particularly expected.[141]

The court considered it to be known in the art that the racemate and each enantiomer individually would show biological activities different from one another -- already by 1954, since the patent application in *Adamson* was filed March 10, 1954.[142] Again, the picture looked bleak for enantiomer patent protection based on *Adamson*, here in terms of showing unexpected results.

134 *Id.*, citing *In re* Lamberti, 545 F.2d 747, 750 (C.C.P.A. 1976), brackets in original.

135 Merck & Co., 874 F.2d at 808-09.

136 *Id.* at 809.

137 35 U.S.C. § 103(a) (2000).

138 Merck & Co., 874 F.2d at 809, citing *In re* Dow Chemical Co., 837 F.2d 469, 473 (Fed. Cir. 1988).

139 Merck & Co., 874 F.2d at 809 footnote.

140 *In re* Adamson, 275 F.2d 952, 955 (C.C.P.A. 1960).

141 *Id.*

142 *Id.* at 952.

However, a few case-limiting statements may be made about the experimental results in *Adamson* and the court's statement about differences being known in the art. First, the toxicity of the racemate was between that of the inactive and active isomers, which the court stated would have been expected. Moreover, the active isomer only showed twice as much activity as the racemate. These *both* would be expected if using a dosage of the active isomer equal to the same dosage of the racemate, which only contains half the amount of active isomer.[143] Therefore, the court's statement that there is a "difference" in activity that would have been expected may be limited to the experimental findings here since the concept of a substantial difference as described by the Karrer reference was not defined by the court or probed by the experimental findings by in fact showing a drastic difference. In other words, along with the difference in toxicity, the difference in activity itself would have been expected, not just that a difference would have existed. Had the biological activity been greatly superior in an enantiomer compared to the racemate, it would appear unlikely that the court would have stated that such a difference would have been expected, which would be in accord with *Wilder* in that similar compounds are expected to have similar properties.

As for the weight to be given evidence of unexpected results when rebutting a *prima facie* obviousness attack, this was outlined in *In re Lohr*.[144] The C.C.P.A. held that

> When a new compound so closely related to a prior art compound as to be structurally obvious is sought to be patented based on the alleged greater effectiveness of the new compound for the same purpose as the old compound, clear and convincing evidence of substantially greater effectiveness is needed.[145]

Therefore, the lower standard of a preponderance of the evidence was ruled out. When weighing purported unexpected results against a *prima facie* showing, the results need to not only weigh more heavily but convincingly so. This sets a greater burden on the patent applicant. Thus, what types of results would be necessary are critically important to consider.

Revisiting *In re Papesch*, the court stated that "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing[,]"[146] and that "There is no basis in law for ignoring any property in making such a comparison [between the claimed compounds and the prior art compounds]. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous."[147] Therefore, all properties must be considered. Questions arise, *e.g.*, as to whether an unexpected superiority of one property is sufficient when there exist similarities of other common properties among the claimed and prior art compounds. As for *Papesch*, the court stated:

143 Darrow, *supra* note 6, ¶ 23 n.64.

144 *In re* Lohr, 317 F.2d 388 (C.C.P.A. 1963).

145 *Id.* at 392.

146 *In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963).

147 *Id.*

> The argument has been made that patentability is here being asserted only on the basis of one property, the anti-inflammatory activity, and that the compounds claimed and the compound of the prior art presumably have many properties in common. Presumably they do, but presumption is all we have here. The same is true of all of the compounds of [cases cited] which were held patentable over compounds of the prior art, many of which must have had more in common by way of properties than the compounds here because the relationships, structurally, were even closer than here.[148]

The above is, at least somewhat, attenuated by subsequent case law[149] as seen in *In re De Montmollin*[150] and *In re Mod*.[151] In *De Montmollin*, the C.C.P.A. found that the ability of claimed compounds to dye cotton in addition to wool did not render the claimed compounds nonobvious over structurally closely related prior art compounds due to common properties with those compounds, which included the dying of wool.[152] The *De Montmollin* court distinguished *Papesch* by stating, "There the only indication of obviousness was such presumption as might arise from the close chemical structural relationship between the compounds claimed and the prior art."[153] Thus, it was only presumed that the claimed compounds of *Papesch* had properties in common with structurally similar compounds,[154] whereas here, similar properties were actually shown. In *Mod*, the C.C.P.A. confirmed *De Montmollin* by finding:

> Inasmuch as the claimed compounds and those of [the prior art] do possess a close structural relationship and it is not denied that they have a specific, significant property in common, *viz.* insecticidal activity, we do not regard the additional antimicrobial activity discovered by appellants for the claimed compounds sufficient ground to hold that the subject matter as a whole is unobvious.[155]

Thus, in *Mod*, it may be stated that the existence of a "new" activity does not outweigh obviousness based on a significant, common activity.

As for stereoisomers, in *In re Anthony*,[156] the applicant conceded in, by the latest, 1969 that

> With respect to claims 11 and 12, directed to the *d*- and *l*-isomers of etryptamine *per se*, appellant acknowledges here that those claims are unpatentable on the record since "under existing law a stereoisomer is not patentable over its known racemic mixture unless it possesses unexpected properties not possessed by the racemic mixture."[157]

148 *Id.* (citations omitted).

149 DONALD S. CHISUM, 2 TREATISE ON THE LAW OF PATENTABILITY, VALIDITY AND INFRINGEMENT § 5.04[6][e][ii] at 5-517 (2007).

150 *In re* De Montmollin, 344 F.2d 976 (C.C.P.A. 1965).

151 *In re* Mod, 408 F.2d 1055 (C.C.P.A. 1969).

152 *In re* De Montmollin, 344 F.2d at 978-79.

153 *Id.* at 978.

154 This presumption is stated in *Wilder supra*.

155 *In re* Mod, 408 F.2d at 1057 (C.C.P.A. 1969) (citation omitted).

156 *In re* Anthony, 414 F.2d 1383 (C.C.P.A. 1969).

157 *Id.* at 1386 (footnote omitted).

Does this mean that enantiomers are *ab initio prima facie* obvious over their racemates? First, this concession does not take into account specifically the nonobviousness of separation and thus any reasonability of expectation of success; and second, how a teaching away would be factored in the analysis was not considered since none was shown. Also, the compounds claimed may have been nonobvious over the prior art in that unexpected results may have existed to rebut *prima facie* obviousness. The results of the experiments that may have shown this were not weighed by the court, however, since the affidavit in which the results were submitted was not submitted under the rules of U.S.P.T.O. practice and thus was not considered.[158]

In *In re Albrecht*,[159]

> The sole issue [was] whether a novel chemical compound is unobvious within the meaning of 35 USC 103 if it is discovered after synthesis to have a new and advantageous property not possessed by a prior art compound, notwithstanding the fact that it may possess a property known to be possessed by the known compound.[160]

The court found the claimed compounds to be nonobvious. *Mod* was distinguished by the *Albrecht* court in that, there, a common property of the claimed compounds was a significant property.[161] *Wilder*, which was decided after *Mod* and *Albrecht*, of course does not change the ruling of *Albrecht*, in that a new property not found in the prior art compounds could not have been presumed to have existed in a compound of similar structure; otherwise, it would not be a new property.

In *In re Nolan*,[162] the C.C.P.A. held that the applicants did not overcome a showing of *prima facie* obviousness although unexpected results were shown[163] for an improvement in a gaseous discharge display/memory device.[164] The unexpected results, the court stated, were not shown in the most significant feature of the invention, whereas other features were in common with the prior art.[165] Therefore, the court weighed the most significant feature most heavily when balancing the *prima facie* obviousness against the unexpected results, as was done in *Mod*. In both cases, commonality in the most significant feature precluded patentability.

Unexpected results in significant properties were seen in *In re May*.[166] Citing *Nolan*, the C.C.P.A. stated that any expected results need to be weighed against any unexpected results.[167] In *May*, novel isomers were claimed in method of use and composition claims,[168] where the composi-

158 *Id.*

159 *In re* Albrecht, 514 F.2d 1389 (C.C.P.A. 1975).

160 *Id.* at 1394.

161 *Id.* at 1396.

162 *In re* Nolan, 553 F.2d 1261 (C.C.P.A. 1977).

163 *Id.* at 1267.

164 *Id.* at 1262.

165 *Id.* at 1267.

166 *In re* May, 574 F.2d 1082 (C.C.P.A. 1978).

167 *Id.* at 1092, citing *In re* Nolan, 553 F.2d at 1267, comparing *In re* Murch, 464 F.2d 1051 (C.C.P.A. 1972) and *In re* Orfeo, 440 F.2d 439 (C.C.P.A. 1971).

168 *In re* May, 574 F.2d at 1084.

tion claims were treated as compound claims by the court.[169] Regarding the method claims, the court found that the *raison d'etre* for research in the area of the claimed compounds was to find a compound with the very property shown by the applicants.[170] Thus, the property was the most significant property, as required by *Nolan*. As for the compound claims, the court cited *Albrecht* for the proposition that a novel compound may be nonobvious even though it has properties in common with structurally similar compounds[171] and cited *Nolan* again stating that expected and unexpected properties must be balanced.[172] Further, the court discussed *Wilder* by stating, "Implicit in [*Wilder*] is that an applicant may rebut the [presumption that compounds similar in structure will have similar properties] by producing sufficient evidence which demonstrates a substantial degree of unpredictability in the pertinent art area."[173] The court found that the applicants "established a substantial record of unpredictability *vis-a-vis* a highly significant combination of properties."[174] Only claimed compounds (five of 21 compounds tested), not those of the prior art or homologues/isomers/racemates of the claimed compounds, were shown to possess no morphine antagonistic activity or a combination of no physical dependence capacity and no morphine antagonistic activity.[175] Therefore, the court held that the claims were nonobvious due to unexpected results in that similar compounds were shown not to have similar properties, which were weighed as the most significant properties by the court.

In *In re Payne*,[176] the C.C.P.A. stated that the rebuttal evidence of unexpected results must be commensurate with the prior art.[177] Here, the applicant did not make a sufficient showing that the properties of the claimed compounds were unexpected against the known prior art and thus could not rebut a showing of *prima facie* obviousness.[178] The applicant in *Payne* argued that the prior art compound used for comparison was "'represented and superior in pesticidal properties to the compounds described in [the prior art].'"[179] Thus, the court requires that a comprehensive comparison be made.

b. Court of Appeals for the Federal Circuit

In *In re Chupp*,[180] unexpected properties were found to rebut *prima facie* obvious-

169 *Id.* at 1093 n.10.

170 *Id.* at 1093.

171 *Id.*, citing *In re* Albrecht, 514 F.2d 1389, 1395-96 (C.C.P.A. 1975).

172 *In re* May, 574 F.2d at 1094; further citing *cf. In re* Murch, 464 F.2d 1051 (C.C.P.A. 1972), *In re* Ruschig, 343 F.2d 965 (1965); and citing to *see generally In re* Papesch, 315 F.2d 381 (1963).

173 *In re* May, 574 F.2d at 1094.

174 *Id.* at 1095.

175 *Id.* It is noted that absence of a property may be evidence of nonobviousness where one of ordinary skill in the art would expect a claimed invention to possess that property. M.P.E.P. at § 716.02(b) III, citing Ex parte Mead Johnson & Co., 227 USPQ 78 (Bd. Pat. App. & Inter. 1985).

176 *In re* Payne, 606 F.2d 303 (C.C.P.A. 1979).

177 *Id.* at 318.

178 *Id.*

179 *Id.* at 316.

180 *In re* Chupp, 816 F.2d 643 (Fed. Cir. 1987).

ness. There, the claimed compound differed from the prior art by only a single methylene group[181] yet gave superior results over the prior art compound as an herbicide in certain crops.[182] The method claims for the compounds as used with those certain crops were allowed.[183] The court stated, "Under the *Papesch* doctrine, evidence of unobvious or unexpected advantageous properties may rebut a *prima facie* case of obviousness based on structural similarities. Such evidence may include data showing that a compound is unexpectedly superior in a property it shares with prior art compounds."[184] The court stated:

> *Papesch* held that a compound can be patented on the basis of its properties, it did not hold that those properties must produce superior results in every environment in which the compound may be used. To be patentable, a compound need not excel over prior art compounds in all common properties. Evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a *prima facie* case of obviousness.[185]

Furthermore, the court distinguished *Payne* by stating that there the applicant did not give a sufficient showing of unexpected results because it was not commensurate with the scope of the prior art in that the claimed compound was compared to too few prior art compounds.[186] Thus, it appears that while any comparison must comprehensively include the prior art and that unexpected properties should be in a significant property, that the new compound is not unexpectedly superior to the prior art compounds in every aspect is of no moment.

Additionally, according to *In re Geisler*,[187] any experiments used to show results in an attempt to rebut *prima facie* obviousness need to show that the results are unexpected, not just superior.[188] However, the Federal Circuit also stated in *Geisler*, citing *In re Soni*, "'When an applicant demonstrates substantially improved results, as Soni did here, and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary.'"[189] Therefore, superior results that are characterized as unexpected (and are convincingly so, *see Lohr supra*) are accepted as such unless the U.S.P.T.O. makes a showing as to why the results are only superior and not unexpected.

Even if unexpected results are found, this does not guarantee nonobviousness. The unexpected results must be weighed against any initial finding of *prima facie* obviousness.[190] Indeed, as was the case in

181 *Id.* at 644.

182 *Id.*

183 *Id.* at 645.

184 *Id.* at 646, citing *In re* Papesch, 315 F.2d 381, 386-87 (citation omitted).

185 *Id.* at 646 (citations omitted).

186 *Id.*

187 *In re* Geisler, 116 F.3d 1465 (Fed. Cir. 1997).

188 *See id.* at 1469-70.

189 *Id.* at 1471, citing *In re* Soni, 54 F.3d 746, 751 (Fed. Cir. 1995).

190 Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1483 (Fed. Cir. 1997).

Richardson-Vicks, the Federal Circuit found that "The unexpected results and commercial success of the claimed invention, although supported by substantial evidence, do not overcome the clear and convincing evidence that the subject matter sought to be patented is obvious."[191] In *Richardson-Vicks*, a combination of two drugs was claimed in a single formulation. The court held that the clear suggestion in the art to combine the drugs outweighed the showing of unexpected synergy between the drugs.[192]

3. Summary

All properties of the claimed and prior art compounds are to be considered. A claimed compound that is similar in structure to prior art compounds is presumed to have similar properties compared to the prior art compounds. Any evidence proffered to rebut the presumption should be clear and convincing. The presumption may be rebutted by any newly found property that the claimed compound exhibits that the prior art compounds do not. However, regardless of any newly found property, if the claimed compound exhibits a significant property in common with the prior art compounds, the presumption is likely not rebutted, even with evidence of unexpected results in other properties. Any results shown should show a comprehensive comparison against the prior art compounds, and the results should not just be superior but unexpected, where the unexpected nature of the results outweighs any *prima facie* showing.

For enantiomers, some racemates may have properties substantially different from the isolated enantiomers; however, it is unlikely that the racemate will not possess some property at least observed to some degree in the individual enantiomers (besides optical activity).[193] However, enantiomers may simply not work well as drugs whereas their racemates may. For example, in *Nolan*, the improvement was to one feature of the invention which was shown to work prior to the improvement. For enantiomeric drugs, the meaning of *Nolan* is likely to be limited in that enantiomers must meet several criteria to work effectively *in vivo* as drugs, *i.e.*, have good solubility, good absorption, slow clearance, low toxicity, ease of formulation, *etc.*; and failure in any one of these may preclude development of an enantiomeric drug over its racemic drug. Thus, the "most significant" feature of the drug may likely be whichever improvement allows the enantiomeric drug to be developed, including the use of a separation process that was nonobvious in itself, as discussed *supra*.

G. Size of Genus

The size of a prior art genus also is a factor when considering whether any species of the genus is patentable over the genus. For enantiomers, the genus is the racemate and the species is the enantiomer for which patent protection is sought. As Darrow states, "Generally speaking, the larger the genus, the less likely that a species within that genus will be held

191 *Id.* at 1484.

192 *Id.* at 1483-84.

193 Also, even if one enantiomer in a mixture possesses all of any desired biological properties whereas a prior art mixture possesses none, the isolated enantiomer with the desired properties may be deemed obvious over the prior art mixture in that its separation was merely purifying away impurities. *See* Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (D.W.Va. 2004), *aff'd*, 161 Fed. Appx. 944 (2005) and Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1295 (Fed. Cir. 2007), discussed *infra*.

obvious, and *vice versa*."[194] The prior art in *Bergel*, discussed *supra*, disclosed a large genus, as did the prior art in *In re Jones*,[195] where the genus was potentially infinite.[196] In both cases, the claimed compounds were found nonobvious. However, Darrow also cautions that it is not clear how small a genus may be before the species are considered obvious over the genus.[197] Indeed, the M.P.E.P. states

> [Examiner's should] consider the size of the prior art genus, bearing in mind that size alone cannot support an obviousness rejection. *See, e.g., [In re] Baird*, 16 F.3d [380,] 383, 29 USPQ2d [(BNA) 1550,] 1552 (observing that "it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved"). There is no absolute correlation between the size of the prior art genus and a conclusion of obviousness. *Id.* Thus, the mere fact that a prior art genus contains a small number of members does not create a *per se* rule of obviousness.[198]

The totality of the circumstances must be considered, and the size of the genus weighed as a factor within those circumstances.

> [A] genus may be so small that, when considered in light of the totality of the circumstances, it would anticipate the claimed species or subgenus. For example, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic chemical formula inherently anticipated a claimed species within the genus because "one skilled in [the] art would... envisage *each member*" of the genus. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962) (emphasis in original).[199]

The size of the genus is particularly important as to the finite obvious-to-try argument. As the genus becomes smaller, the number of possible starting points also decreases, making it more obvious-to-try variations of what is already known. An enantiomer containing a single stereogenic center has a genus of only two, and the structure of each species can be determined from the genus. However, again, the size of the genus is only one factor in the analysis, and even for a genus of two, the presence or absence of other (non)obviousness factors may be dispositive (as was seen, *e.g.*, in *Williams* and *Adamson supra*).

H. Case-In-Point: *Ortho-McNeil v. Mylan*

A relatively recent district court case involving enantiomers of a racemic drug and later affirmed by the Federal Circuit,[200] *Ortho-McNeil*[201] presents a case-in-point to bring together aspects previously discussed in this paper. The

194 Darrow, *supra* note 6, ¶ 26, and citations therein.

195 *In re* Jones, 958 F.2d 347 (Fed. Cir. 1992).

196 *Id.* at 350.

197 Darrow, *supra* note 6, ¶ 26, and citations therein.

198 M.P.E.P. at § 2144.08 II(A)(4)(a).

199 *Id.*

200 Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (D.W.Va. 2004), *aff'd*, 161 Fed. Appx. 944 (2005).

201 *Id.*

claimed drug in the case is a racemate containing two enantiomers,[202] thus having a genus of two. However, the district court reiterated that a court must make *Graham* factual inquiries in every case.[203] This, then, the court cautioned, precludes an *ab initio* finding that any enantiomers are *prima facie* obvious over the racemate.[204] Thus, the state-of-the-law at the time *Ortho-McNeil* was decided was that enantiomers are not *prima facie* obvious over there racemates simply because they are enantiomers, even with a small genus of two. All obviousness factors, including process of resolution, must be weighed.

However, in this case, a *prima facie* situation was indeed found. The district court found that motivation existed in the prior art to isolate the enantiomers since the prior art taught of greater potency (*i.e.*, a more desirable property) of one enantiomer over the other and that one enantiomer was regarded in the art as being an impurity without activity.[205] Also, although the separation proved to be difficult in this instance and was not routine, according to the district court, the prior art still enabled one of ordinary skill in the art to resolve the racemate.[206] Therefore, the process of separation was obvious, and there was a reasonable expectation of success to obtain the enantiomers from the racemate.[207] Therefore, a *prima facie* case was made. Indeed, although the district court stated that the standard is not one of being obvious-to-try,[208] the court cited *In re Eli Lilly*[209] (citing *O'Farrell*) to summarize what is the non-finite obvious-to-try scenario.[210] Thus, the *prima facie* showing here could be characterized as a finite obvious-to-try situation.

However, in addition to finding secondary considerations weighing in favor of nonobviousness,[211] the district court found that here "[u]nexpected results alone successfully rebut a *prima facie* case of obviousness, if so established by the enantiomer *per se* of structural similarity."[212] Thus, the unexpected properties rebutted the presumption that structurally similar compounds have similar properties. Here, greater solubility was found, as well as unexpected effectiveness against *S. pneumoniae*.[213] Also, the

202 *Id.* at 721.

203 *Id.* at 749 n. 19.

204 *Id.*

205 *Id.* at 752.

206 *Id.* at 753.

207 It is noted that the court states later that there would have been no reasonable expectation of success of obtaining the claimed enantiomer *with the enantiomer's demonstrated properties*. *Id.* at 753-55. However, the court later analyzes the properties as unexpected properties. Therefore, the court incorrectly applied the reasonable expectation of success standard in relation to *prospectively* obtaining the compound, which should be done without regard to the properties of the compound. Indeed, reasonable expectation of success weighs in whether a *prima facie* obvious situation exists, which is a prospectively-looking analysis. With the presumption that similar compounds have similar properties, *see supra*, unexpected results are just that, unexpected and should never be *ab initio*. If anything, finding a better compound is what would give a motivation to obtain such a compound. As shown, there was a reasonable expectation of success in producing the compound. Therefore, the incorrect application is harmless error.

208 Ortho-McNeil Pharm., 348 F. Supp. 2d at 752.

209 *In re* Eli Lilly & Co., 902 F.2d 943, 945 (Fed. Cir. 1990).

210 Ortho-McNeil Pharm., 348 F. Supp. 2d at 752.

211 *Id.* at 756-60.

212 *Id.* at 760-61.

213 *Id.* at 755-56.

prior art taught greater activity usually was accompanied by greater toxicity, whereas here greater activity was shown as well as lower toxicity.[214] Therefore, although no *ab initio prima facie* obviousness exists for enantiomers over their racemates, even if such a *per se* rule were to exist, unexpected results can be used to overcome such a showing.

*I. Pre-*KSR *Non-Rigid Application of the TSM Test by the Federal Circuit*

As shown *supra*, motivation is one element of the overall obviousness test. The Federal Circuit developed the teaching, suggestion, motivation ("TSM") test to determine whether this element is satisfied,[215] where a teaching, suggestion, or motivation in the prior art is to modify the existing prior art to arrive at the claimed invention. The Supreme Court in *KSR* stated that the Federal Circuit applied this test too rigidly.[216] However, *KSR* is an anomalous Federal Circuit case, and the Supreme Court in *KSR* simply told the Federal Circuit to follow its own precedent. Indeed, the Federal Circuit applied the test flexibly prior to *KSR*.

In *Alza*,[217] the Federal Circuit stated:

> Our court's analysis in *Kahn* bears repeating: A suggestion, teaching, or motivation to combine the relevant prior art teachings *does not have to be found explicitly in the prior art*, as "the teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art."[218]

The court also stated, "There is flexibility in our obviousness jurisprudence because a motivation may be found implicitly in the prior art. We do not have a rigid test that requires an actual teaching to combine before concluding that one of ordinary skill in the art would know to combine references."[219]

The above is supported in *Dystar*.[220] There, the Federal Circuit stated:

> In contrast to the characterization of some commentators, the suggestion test is not a rigid categorical rule. The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the

214 *Id.* at 755. It is noted that the court here found that, "Although the prior art certainly indicates that one enantiomer is often more therapeutically active than the other, it does not teach that the more active enantiomer is consistently twice as potent as the racemate." *Id.* at 754. As is the case here, this would be the expected situation if one enantiomer is inactive, as discussed *supra*. *See* Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1295 (Fed. Cir. 2007), discussed *infra* at page 55, finding that such activity results are expected. Here, since there are other unexpected results (*e.g.*, greater solubility), the district court could still have found in favor of nonobviousness.

215 KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007).

216 *Id.* at 1739.

217 Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286 (Fed. Cir. 2006).

218 *Id.* at 1291, citing *In re* Kahn, 441 F.3d 977, 987-88 (Fed. Cir. 2006) (additional citations omitted) (emphases in original).

219 Alza Corp., 464 F.3d at 1291.

220 Dystar Textilfarben GmbH v. C.H. Patrick Co., 464 F.3d 1356 (Fed. Cir. 2006), *cert. denied*, 127 S.Ct. 2937 (2007).

> nature of the problem itself. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). As we explained in *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997), "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."[221]

Indeed, as the above excerpt demonstrates, the Federal Circuit has been applying its test in this manner for many years. Furthermore, the court stated, "It is difficult to see how our suggestion test could be seen as rigid and categorical given the myriad cases over several decades in which panels of this court have applied the suggestion test flexibly[,]"[222] and "Our suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense."[223]

Therefore, the Federal Circuit has been applying its TSM test non-rigidly throughout its jurisprudence. Furthermore, the Federal Circuit has required that the test be applied flexibly by the lower courts. Again, *KSR* was an anomalous case since the Federal Circuit applied its own precedent incorrectly, and the Supreme Court reversed the Federal Circuit and cautioned against the rigid application of the TSM test.[224] Therefore, again, the Supreme Court was simply telling the Federal Circuit to follow its own precedent.

J. Case-in-Point: *Pfizer v. Apotex*

Another case-in-point is *Pfizer*,[225] decided by the Federal Circuit even more recently than *Ortho-McNeil* and only about a month prior to the Supreme Court's decision in *KSR*. Although *Pfizer* does not involve enantiomers, it is a chemical compound case that illustrates well the elements of the test for obviousness. Furthermore, after *KSR*, the Federal Circuit denied rehearing *en banc* for this case,[226] which demonstrates that the court believes the obviousness doctrine followed in this case was based upon prior precedent.

Pfizer developed amlodipine and discovered that it has anti-hypertensive and anti-ischemic pharmacological properties.[227] A patent was granted for amlodipine and certain pharmaceutically acceptable salts (not including besylate), where maleate was described as the best salt ("the '909 patent").[228] However, the maleate salt was susceptible to degradation and stickiness, making it hard to formulate the drug as a tablet.[229] Upon further testing, Pfizer found that the anionic besylate (*i.e.*, benzene sulphonate) salt of amlodipine proved to have superior sta-

221 *Id.* at 1361.

222 *Id.* at 1367.

223 *Id.* (citation omitted).

224 KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007).

225 Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007), *reh'g denied*, 488 F.3d 1377 (Fed. Cir. 2007), *cert. denied*, 2007 U.S. LEXIS 11016 (2007).

226 *Id.*

227 Pfizer, Inc., 480 F.3d at 1353.

228 *Id.*

229 *Id.* at 1353-54.

bility and non-stickiness.[230] Another patent application was filed on the besylate salt, but the claims to the new salt were rejected as obvious over the '909 patent and other prior art, including Berge.[231] Berge, a published article, showed a table of "53 FDA-approved, commercially marketed anions, including benzene sulphonate, that are useful for making pharmaceutically-acceptable salts," and showed that, at the time of the printing of the reference, besylate had a frequency of use of 0.25%.[232] After filing a continuation application, the rejection was maintained. Pfizer then filed a declaration that argued that amlodipine besylate has an unexpected combination of properties.[233] The rejection was then withdrawn, and the application issued as a patent.[234]

Apotex filed an A.N.D.A. to amlodipine besylate, and Pfizer sued for infringement under the besylate patent.[235] The district court found that the besylate salt of amlodipine would not have been obvious to one of ordinary skill in the art, stating Berge gave no motivation to select besylate due to its low frequency of use and gave no expectation of success due to the unpredictability of the influence that a particular salt has on a compound.[236] Furthermore, the district court found that the besylate form was unexpectedly superior to the other amlodipine salts of the prior art.[237]

The Federal Circuit disagreed and reversed the district court. Pfizer had argued: (1) the '909 patent did not suggest or motivate a POSITA to make amlodipine besylate because none of the listed anions in the '909 patent have cyclic structures as besylate; (2) even if the '909 patent were combined with Berge, a POSITA would not have been motivated to make amlodipine besylate since Berge showed a low frequency of use of besylate; and (3) other prior art cited was not relevant since examples of besylate salts disclosed therein are limited to pharmaceuticals unrelated to amlodipine.[238] As to the first point, the court replied:

> We reject Pfizer's first argument, since a suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather "may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *DyStar*, 464 F.3d at 1361; *see also Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1307-08 (Fed. Cir. 2006).[239]

Thus, again, the Federal Circuit reiterated that the TSM test is a flexible test. Furthermore, the court stated that it is irrelevant that none of the anions in the

230 *Id.* at 1354.

231 *Id.* at 1355.

232 *Id.*

233 *Id.* at 1355-56.

234 *Id.* at 1356.

235 The first amlodipine patent had expired by this time. *See id.* at 1352.

236 *Id.* at 1356-57.

237 *Id.* at 1357.

238 *Id.* at 1361-62.

239 *Id.* at 1362.

'909 patent do not have cyclic structures. Rather, one must look at the prior art as whole, including the nature of the problem to be solved, which here included replacing maleate with another salt species since the double bond in maleate is reactive and susceptible to degradation.[240] As for the second point, the court found that, to replace the maleate, a POSITA would have used other salts that were already known as pharmaceutically-acceptable salts of other drugs and would not have made a novel salt; thus a POSITA would have started with the anions of Berge.[241] Furthermore, the 0.25% frequency of use was not probative since Berge also shows that forty out of the fifty-three F.D.A.-approved anions were used in less than 1% of drugs, with a precipitous drop-off after HCl, which had a frequency of use of 43%.[242] As for the third point, the court found that the other prior art described desirable properties of besylate.[243] Additionally, Pfizer conceded (*e.g.*, by showing bioequivalence for an F.D.A. submission[244]) that the besylate part of the drug has no therapeutic effect, merely serves as a means for delivering amlodipine to the body, and that it was only chosen for improved physical properties.[245] Therefore, it did not matter that besylate was not described for use in a drug with the same indication as amlodipine.[246] All of this showed that there was sufficient motivation in the prior art to develop the besylate form of amlodipine.[247]

Regarding a reasonable expectation of success, the court stated that the district court found none due to unpredictability in the art, which is not the law.[248] Citing *Merck v. Biocraft* and *O'Farrell*, the court reiterated that the expectation of success is not absolute, but reasonable.[249] The Federal Circuit concluded that the prior art would have given a reasonable expectation of success, and Pfizer stated in another litigation against a generic that amlodipine acts the same in the body as a maleate or a besylate salt.[250]

Pfizer argued "that if anything, amlodipine in its besylate salt form would at most be 'obvious-to-try,' *i.e.*, to vary all parameters or try each of numerous possible choices to see if a successful result was obtained."[251] Thus, Pfizer argued that this would have been an impermissible non-finite obvious-to-try situation. The court responded that each case must be decided on its own facts. "Undue dependence on mechanical application of a few maxims of law, such as 'obvious-to-try,' that have no bearing on the facts certainly invites error as decisions on obviousness must be narrowly tailored to the facts of each individual case."[252] Furthermore, the court made the following findings:

240 *Id.*

241 *Id.* at 1362-63.

242 *Id.* at 1363.

243 *Id.*

244 *Id.* at 1354-55.

245 *Id.* at 1363.

246 *Id.*

247 *Id.* at 1364.

248 *Id.*

249 *Id.* (citations omitted)

250 *Id.* at 1365.

251 *Id.*, citing *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

252 *Id.* at 1366.

First, this is not the case where there are "numerous parameters" to try. Rather, the only parameter to be varied is the anion with which to make the amlodipine acid addition salt. Although we recognize some degree of unpredictability of salt formation, *see, e.g., Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1379 (Fed. Cir. 2006), the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious.[253]

Second, this is not the case where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903; *Medichem*, 437 F.3d at 1167.[254]

Finally, Pfizer protests that a conclusion that amlodipine besylate would have been obvious disregards its "discovery" because it was obtained through the use of trial and error procedures. While the pharmaceutical industry may be particularly adversely impacted by application of an "obvious-to-try" analysis, *see, e.g., In re Merck*, 800 F.2d at 1100 (Baldwin, J., dissenting), that Pfizer had to verify through testing the expected traits of each acid addition salt is of no consequence because it does not compel a conclusion of non-obviousness here.[255]

The court noted that the manner of invention shall not negative patentability, as required by section 103, but that

> [O]n the particularized facts of this case, consideration of the "routine testing" performed by Pfizer is appropriate because the prior art provided not only the means of creating acid addition salts but also predicted the results, which Pfizer merely had to verify through routine testing. *Merck*, 874 F.2d at 809.[256]

The court also found that the case was analogous to optimization.

> We find this case analogous to the optimization of a range or other variable within the claims that flows from the "normal desire of scientists or artisans to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (determining where in a disclosed set of percentage ranges the optimum combination of percentages lies is prima facie obvious).[257]

Finally, no unexpected results were shown.[258] Furthermore, even if unexpected results were shown, the court stated that they would not have overcome the strong showing of (*prima facie*) obviousness. "Alternatively, we hold that even if Pfizer showed that amlodipine besylate exhibits unexpectedly superior results,

253 *Id.*

254 *Id.*

255 *Id.* at 1366-67.

256 *Id.* at 1367.

257 *Id.* at 1368.

258 *Id.* at 1370-71.

this secondary consideration does not overcome the strong showing of obviousness in this case."[259]

Therefore, through a flexible application of the TSM test, there would have been a motivation and a reasonable expectation of success to produce the besylate salt of amlodipine. Also, there were a limited number of choices from which a POSITA could start, and the methods used to arrive at the besylate form would have been within the POSITA's grasp, making this a finite obvious-to-try situation. The finite obvious-to-try case was so strong here as to preclude any unexpected results from rebutting it.

III. *KSR*

KSR concerned a combination patent directed to an adjustable pedal assembly with electric throttle control.[260] The claimed invention included an electric sensor placed on the pivot point of an adjustable accelerator pedal. The sensor detected the position of the pedal and communicated this information to a computer to control the amount of fuel injected into the engine, thus controlling a vehicle's speed.[261] The Supreme Court reversed the Federal Circuit and agreed with the district court by finding that the claimed invention would have been obvious to one of ordinary skill in the art.

The Supreme Court stated that the Federal Circuit applied its TSM test too rigidly. The Federal Circuit in its decision stated that the district court was not strict enough in regard to the TSM test. The Supreme Court summarized:

> With principal reliance on the TSM test, the Court of Appeals reversed. It ruled the District Court had not been strict enough in applying the test, having failed to make "'finding[s] as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of [the] invention' . . . to attach an electronic control to the support bracket of the Asano assembly." 119 Fed. Appx., at 288 (brackets in original) (quoting *In re Kotzab*, 217 F.3d 1365, 1371 (CA Fed. 2000)).[262]

The Supreme Court found that the Federal Circuit required that the prior art specifically discuss the very problem the invention was meant to solve.

> The Court of Appeals held that the District Court was incorrect that the nature of the problem to be solved satisfied this requirement 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.[263]

The Supreme Court disagreed. "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

259 *Id.* at 1372.

260 KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007).

261 *Id.* at 1736.

262 *Id.* at 1738.

263 *Id.*, citing Teleflex, Inc. v. KSR Int'l Co., 119 Fed. Appx. 282, 288 (Fed. Cir. 2005).

expansive and flexible approach inconsistent with the way the Court of Appeals applied its TSM test here."[264] In its ruling, the Court did not alter the TSM test and praised its inception. "When 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."[265] However, the Court cautioned against rigid, formulistic application of the test.

> 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.[266]

Therefore, the Supreme Court simply agreed with the previous precedents as followed by the Federal Circuit. Indeed, the Court stated,

> We note the Court of Appeals has since elaborated a broader conception of the TSM test than was applied in the instant matter. *See, e.g., DyStar Textilfarben GmbH & Co. Deutschland KG v. C. H. Patrick Co.*, 464 F.3d 1356, 1367 (2006) ("Our suggestion test is in actuality quite flexible and not only permits, but requires, consideration of common knowledge and common sense"); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (2006) "There is flexibility in our obviousness jurisprudence because a motivation may be found implicitly in the prior art. We do not have a rigid test that requires an actual teaching to combine . . ."). Those decisions, of course, are not now before us and do not correct the errors of law made by the Court of Appeals in this case. The extent to which they may describe an analysis more consistent with our earlier precedents and our decision here is a matter for the Court of Appeals to consider in its future cases. What we hold is that the fundamental misunderstandings identified above led the Court of Appeals in this case to apply a test inconsistent with our patent law decisions.[267]

Furthermore, the Supreme Court stated that finite obvious-to-try may be a permissible basis to determine that an invention would have been obvious. The Court stated that the Federal Circuit rejected that the invention would have been obvious under the obvious-to-try rationale: "That it might have been obvious-to-try the combination of Asano and a sensor was likewise irrelevant, in the court's view, because "'"[o]bvious-to-try' has long been held not to constitute obviousness." [*Teleflex, Inc.*, 119 Fed. Appx.] at 289 (quoting *In re Deuel*, 51 F.3d 1552, 1559 (CA Fed.

264 *Id.* at 1739.

265 *Id.* at 1741 (citations omitted).

266 *Id.*

267 *Id.* at 1743.

1995))."[268] The Supreme Court then reiterated what was previously developed in the case law.

> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious-to-try." 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. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious-to-try might show that it was obvious under § 103.[269]

When there is a finite number of possibilities from which to start, a technique that is within the grasp of a POSITA is used to modify the prior art to arrive at the claimed invention, and the results are not unexpected, the invention is obvious. This is the finite obvious-to-try situation. Here, the Supreme Court found that there was no teaching away[270] and that the secondary considerations presented in the case did not overcome the strength of the *prima facie* showing of obviousness.[271]

The Supreme Court's unanimous decision in *KSR* did not substantively change the law of obviousness and only directed the Federal Circuit to follow its own precedent. Thus, the case is an anomaly because Federal Circuit deviated from its precedent when it decided the case. As shown *supra*, *Alza*, *Dystar*, and *Pfizer* are pre-*KSR* cases decided not long before *KSR* in which the TSM test was applied flexibly. Also, as shown *supra*, *In re Merck*, *Merck v. Biocraft*, *Ortho-McNeil*, and *Pfizer* presented the finite obvious-to-try situation before the Supreme Court found that such a rationale would be permissible in *KSR*, where Ortho-McNeil overcame obviousness by sufficiently showing unexpected results. However, the *prima facie* case was so strong in *Pfizer* that the presumption of obviousness could not be overcome. Therefore, *KSR* did not substantively change the law of obviousness.[272]

IV. Post-*KSR*

Several cases after *KSR* highlight the state-of-the-law and how the law has not substantively changed due to *KSR*. They also nicely present the elements of obviousness as cases-in-point. These cases include *Sanofi-Synthelabo*,[273] *Forest*,[274] and *Aventis*.[275]

A. Sanofi-Synthelabo v. Apotex

This case is a district court case concerning the patentability of enantiomers. The

268 *Id.* at 1739.

269 *Id.* at 1742 (citations omitted).

270 *Id.* at 1745.

271 *Id.*

272 Horwitz, *supra* note 12; *High Court's Patent Ruling on Obviousness was not Paradigm Shift, Judges Agree*, Patent, trademark & Copyright Law Daily (Oct. 10, 2007).

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

274 Forest Labs., Inc. v. Ivax Pharms., Inc., 501 F.3d 1263 (Fed. Cir. 2007).

275 Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293 (Fed. Cir. 2007).

patent to Sanofi-Synthelabo claims the drug Plavix®, which was approved by the F.D.A. "for the reduction of thrombotic events such as heart attacks and strokes for patients who have recently suffered those events or who have arterial disease or acute coronary syndrome."[276] The active pharmaceutical ingredient ("A.P.I.") of Plavix® is clopidogrel bisulfate, a *d*-enantiomer.[277] Apotex filed an A. N. D. A. to this A.P.I. and Sanofi sued for infringement. The patent claims directed to the compound were found to be nonobvious over the prior art.[278]

The court found that one of ordinary skill in the art would not have had motivation to produce clopidogrel bisulfate. However, the court found that a *prima facie* obvious case was made simply by the prior art showing the racemate, that racemates may be resolved, and the resolved enantiomers may possess different properties.

> For purposes of analysis, the Court assumes that Apotex has made a *prima facie* case of obviousness of the dextrorotatory enantiomer of PCR 4099 in view of the disclosure of the racemate in the '596 patent and the prior art teachings that (1) racemic compounds may be separated into their enantiomers; and (2) those enantiomers, if obtained, may exhibit different biological activity or different degrees of the same type of biological activity exhibited by the racemate.[279]

Thus, is the state-of-the-law such that enantiomers are *prima facie* obvious over their racemates? First, the court *assumed* this to be the case but finds unexpected results to rebut it. Second, other Federal Circuit cases, such as *Pfizer*, caution against this assumption. Furthermore, the district court continued by stating:

> In this regard, the [District] Court concludes that the prior art did not enable a person of ordinary skill in the art to predict with a reasonable expectation of success whether one enantiomer of PCR 4099 would have better pharmaceutical properties than the racemate itself, whether one enantiomer would have all of the activity and none of the toxicity of the racemate as a whole, or whether a single enantiomer would have both all of the activity and all of the toxicity. Moreover, the prior art would not have made obvious whether an isolated enantiomer of PCR 4099 would racemize in the body, serving to neutralize the gains achieved by separating the enantiomers.[280]

Thus, there would have been no motivation to resolve the racemate. Therefore, a *prima facie* case for obviousness could not have been properly made without some form of motivation. Thus, here, even though the court assumed a *prima facie* obvious situation, the court also reasoned that a *prima facie* showing was not made. Another interesting point is that racemization played a role in the court's analysis, as stated in the quote *supra*. As stated by the court, the potential for *in vivo* racemization vitiates any possible gains

276 Sanofi-Synthelabo, 492 F. Supp. 2d at 356.

277 *Id.*

278 *Id.* at 392.

279 *Id.* at 390. "PCR 4099" is the racemate that includes clopidogrel. *Id.* at 366.

280 *Id.* at 390. It appears that the court also improperly grouped together reasonable expectation of success and unexpected results, as was done in *Ortho-McNeil*, discussed *supra*.

from the resolution of a single enantiomer. This also supports that a *prima facie* obvious situation did not exist. Finally, the court stated that separation of the enantiomers would not have been obvious.[281] If so, there would have been no reasonable expectation of successfully obtaining the claimed compound, precluding a finding of *prima facie* obviousness. Even assuming, as did the court, that a *prima facie* case was made, the court found that the clopidogrel bisulfate shows unexpected properties, rendering the invention nonobvious.[282]

The court distinguished this case from *Pfizer*.

> First, the chemists in *Pfizer* were able to identify the structural feature of the maleate salt that was causing problems, and, with that knowledge, were able to produce a short list of salts that they expected to solve the problem. In this case, importantly and by contrast to the situation in *Pfizer*, there were no structural features that would have guided Sanofi chemists in avoiding or selecting any specific acid.[283]
>
> Second, in *Pfizer*, the Federal Circuit noted that several prior art references, including patents, specifically suggested to a person of ordinary skill in the art that the use of the besylate salt would offer improved stability in the particular compound at issue. [...] Here, there was no prior art teaching that the bisulfate salt was particularly likely to be a successful salt form of clopidogrel, and additional prior art - such as the Gould reference - might actually have led the person of ordinary skill in the art away from sulfuric acid, at least as an initial matter.[284]

Also, the court found that the genus of compounds within the prior art from which to choose possible starting compounds was in the millions.[285] If anything, this situation was a non-finite obvious-to-try situation that can not support a *prima facie* showing.

B. Forest v. Ivax

This is a Federal Circuit decision that also involved enantiomers and found that the claimed enantiomers would have been nonobvious. Forest developed the drug escitalopram, which is the (+) isomer of citalopram.[286] The district court found "that one of ordinary skill in the art at the time of the invention would generally have been motivated to develop new compounds rather than undertake the difficult and unpredictable task of resolving a known racemate."[287] Also, the district court found that the method used to separate enantiomers, which was high performance liquid chromatography, was new and unpredictable and difficult to separate the claimed enantiomers, and would give no reasonable expectation of successfully obtaining the claimed enantiomer.[288]

The Federal Circuit agreed with the district court and found for Forest.

281 *Id.*

282 *Id.* at 390-91.

283 *Id.* at 391.

284 *Id.*

285 *Id.* at 362-63.

286 Forest Labs., Inc. v. Ivax Pharms., Inc., 501 F.3d 1263, 1265 (Fed. Cir. 2007).

287 *Id.* at 1267.

288 *Id.* at 1266-67.

Therefore, it appears that there is no presumption that enantiomers are obvious over their racemates, especially when the method of resolution is nonobvious.

C. Aventis v. Lupin

This case involved a separation of two stereoisomers of ramipril,[289] an agiotensin-converting enzyme inhibitor.[290] Ramipril has five stereogenic carbon centers.[291] Since each stereogenic center can have an absolute configuration of *R* or *S*, as shown *supra*, the stereoisomers can be represented as *RRRRR* ("5*R*"), *SSSSR*, *RRSSS*, *SSSSS* ("5*S*"), *etc.*[292] The Federal Circuit found that the prior art included a mixture of the 5*S* and *SSSSR* stereoisomers.[293]

The Federal Circuit found that the predecessor compound of ramipril, enalapril, which has three stereogenic centers, and all the most active pertinent isomers in the prior art, were all in the full *S* configuration.[294] The prior art also taught how to separate enalapril.[295] Relying on *KSR*, the Federal Circuit reversed the district court's finding of nonobviousness in that an explicit teaching to purify the 5*S* stereoisomer was not required. However, this is just the flexible approach that the Federal Circuit stated in, *e.g.*, *Alza*, *Dystar*, and *Pfizer*.

The Federal Circuit stated:

> The analysis is similar where, as here, a claimed composition is a purified form of a mixture that existed in the prior art. Such a purified compound is not always *prima facie* obvious over the mixture; for example, it may not be known that the purified compound is present in or an active ingredient of the mixture, or the state of the art may be such that discovering how to perform the purification is an invention of patentable weight in itself.[296]

Thus, an enantiomer is not *ab initio prima facie* obvious over its racemate, and the nonobviousness of the resolution itself plays a role in the analysis.

> However, 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 purified compound is *prima facie* obvious over the mixture even without an explicit teaching that the ingredient should be concentrated or purified.[297]

Therefore, if there is a motivation to resolve the mixture, then an enantiomer is *prima facie* obvious over the prior art.

289 Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1297-98 (Fed. Cir. 2007).

290 *Id.* at 1296.

291 *Id.* at 1295.

292 *Id.*

293 *Id.* at 1297-98, 1300.

294 *Id.* at 1296-97, 1299.

295 *Id.* at 1297.

296 *Id.* at 1301.

297 *Id.*, citing *In re* May, 574 F.2d 1082, 1090-94 (C.C.P.A. 1978) (holding isolated stereoisomer nonobvious over racemate of stereoisomers, after conceded prima facie showing of obviousness, because isolated stereoisomer was unexpectedly nonaddictive); *In re* Adamson, 275 F.2d 952, 954-55 (C.C.P.A. 1960) (holding isolated stereoisomer obvious over racemate of stereoisomers, given insufficient showing of any unexpected result); and *In re* Merz, 97 F.2d 599, 601 (C.C.P.A. 1938)

The Federal Circuit found that the separation of the 5*S* stereoisomer from the *SSSSR* was within the grasp of the POSITA based on the prior art available.[298] The Federal Circuit also found that no unexpected results were shown: Aventis showed that the 5*S* compound was 18 times more potent than the next most potent isomer; but the Federal Circuit stated that the comparison should be the 5*S* compound over the 5*S*/*SSSSR* mixture, which only showed that one active isomer had most of the activity and the other isomer was mostly inert and that removal of the mostly inert isomer would improve the activity of the active isomer linearly with concentration.[299] Thus, this is similar to purifying away an impurity.

Therefore, this case represents the finite obvious-to-try situation with a finite number of starting choices (here a single racemate of two isomers), motivation to resolve, a resolution technique within the grasp of the POSITA giving a reasonable expectation of successfully obtaining the isomers, where unexpected results did not sufficiently rebut the *prima facie* obviousness showing.

V. Conclusions

The current state-of-the-law is that, even though structurally similar compounds are presumed to have similar properties, there is no *ab initio* presumption of *prima facie* obviousness of enantiomers over their racemates. *KSR* was an anomalous case in that the Federal Circuit had applied its TSM test flexibly prior to *KSR*. Therefore, the Supreme Court was simply reminding the Federal Circuit to follow its own precedent. Prior to *KSR*, finite obvious-to-try has long been a permissible ground for establishing a *prima facie* obvious case, where non-finite obvious-to-try has not.

As for enantiomers, it appears that motivation at least exists to resolve pharmaceutical racemates due to F.D.A. policy. Also, as the state-of-the-art progresses, it is likely that *prima facie* obviousness will be more easily shown, especially considering that enantiomers are usually within a small racemate genus. However, an applicant should not concede a *prima facie* showing and should attempt to attack such a showing in case a strong showing is made, which may otherwise preclude consideration of unexpected results. Thus, an applicant should attempt to find any teaching away that discourages resolution or use of a particular enantiomer. Also, any showing that the only method found to resolve the racemate was itself nonobvious would weigh heavily toward nonobviousness, as well as showing that the enantiomer racemizes readily in the body. These factors may negate any showing of *prima facie* obviousness, and thus unexpected results may not even need to be presented.

In order to show unexpected results, an applicant should try to show clear and convincing evidence that the claimed enantiomer has not only superior properties but unexpected properties. Thus, evidence of how the properties are unexpected would be required. Also, evidence of properties that are dissimilar to any prior art compounds, especially a finding of new properties, rebuts the presumption that similar compounds have similar

298 Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1302 (Fed. Cir. 2007).

299 *Id.*

properties. A showing of a new utility, although potentially difficult for enantiomers of an established racemate drug, would also weigh toward nonobviousness. A comprehensive showing commensurate with the compounds of the prior art must be shown; however, showing that few properties of the claimed enantiomer are shared with compounds of the prior art and that these few shared properties are not significant properties for the claimed enantiomer would be evidence of nonobviousness. Showing that the unexpected properties are the most significant feature of the claimed enantiomers would also help, and showing that the other enantiomers within the racemate are not simply impurities (*i.e.*, have some activity, or, better, have some negative quality) would weigh toward nonobviousness. Finally, not discussed in detail in this paper, a showing of other secondary considerations as defined by *Graham* would help.

A final word about *KSR* -- as stated *supra*, some have opined that *KSR* changed the law of obviousness.[300] Others have stated that, due to *KSR*, more patents are being found invalid.[301] However, others have stated that the law has not changed;[302] and others have determined that *KSR* has not made it more difficult to obtain a patent.[303] It is the position of the author that the law has not substantively changed, as shown throughout this paper. What has changed is that there is a heightened awareness of obviousness law and a rediscovery of the finite obvious-to-try rationale, which was present in the case law well before *KSR*. Finally, as for enantiomers, it is likely that more enantiomers will be found obvious over their racemates, simply due to the progression of science.

300 Cocca and Lewis, *supra* note 11.

301 Jesse Greenspan, *KSR Leads to Increase in Obviousness Invalidations*, IPLAW360, Oct. 25, 2007, http://ip.law360.com/Secure/ViewArticle.aspx?id=37802.

302 Horwitz, *supra* note 12; *High Court's Patent Ruling on Obviousness was not Paradigm Shift, Judges Agree*, Patent, Trademark & Copyright Law Daily (Oct. 10, 2007).

303 Sarah Herbert & Charles Tansey, *Is a U.S. Patent More Difficult to Obtain after KSR?*, IPLaw360, Dec. 5, 2007, http://ip.law360.com/Secure/ViewArticle.aspx?id=41679.