THE PATENTABILITY OF CHIRAL DRUGS POST-*KSR*: THE MORE THINGS CHANGE, THE MORE THEY STAY THE SAME

By Miles J. Sweet

Perhaps more than most, the pharmaceutical industry is dependent on patent protection. The commercialization of discoveries and inventions related to new drugs and therapeutics must necessarily operate within the regulatory frameworks governing health and safety. This inherently public disclosure precludes protection of valuable intellectual property by alternative means such as trade secret. Consequently, there is a rich history of jurisprudence related to patentability in the chemical arts, as the issues surrounding novelty and obviousness often serve as central points of contention in patent infringement litigation.

This Note examines the Federal Circuit's approach to the patentability of an important class of pharmaceutical products known as chiral drugs—drugs based on enantiomers—particularly in view of the standard for determining nonobviousness expressed by the Supreme Court in *KSR International Co. v. Teleflex Inc*.[1] Part I introduces the basic concept of chirality and its significance to the pharmaceutical industry.

Part II addresses the doctrines of novelty and nonobviousness related to enantiomers, focusing on the touchstone of structural similarity and the requirements related to motivation established in pre-*KSR* case law. The cases show that an enantiomer is patentable over its previously disclosed racemate with respect to novelty, but that there is no easy conclusion with respect to nonobviousness.

Part III considers the lessons stemming from a number of recent post-*KSR* decisions on the obviousness of chiral drugs. First, the difficulties associated with resolving racemic mixtures and unexpected properties are critical to preserving the nonobviousness of enantiomers. Second, the mere desirability and knowledge of the potential therapeutic advantages that single-enantiomer drugs may hold have not been held as adequate motivation to employ known separation techniques on disclosed racemic mix-

1. 127 S. Ct. 1727 (2007).

tures. Even in the face of mounting market and regulatory pressure to resolve racemates to their constituent enantiomers, courts have upheld chiral drugs as nonobvious where a patentee effectively demonstrates secondary considerations to overcome a challenge of invalidity based on a prima facie case under 35 U.S.C. § 103.

Part IV concludes that *KSR* has not resulted in a major change in the substantive standard of nonobviousness related to enantiomers, but that patentees should be vigilant in documenting the unpredictability of their work and the evidence of experimental failure in order to rebut an assertion of obviousness.

I. THE CHEMISTRY OF CHIRAL DRUGS

This Part provides a technical primer on the basics of stereochemistry and the concept of chirality, including its biological implications and significance to the pharmaceutical industry.

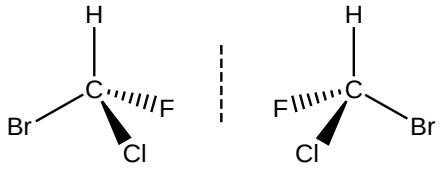
A. Stereochemistry

Chirality is a property of asymmetry related to three-dimensional structure. Human hands represent a special illustration of chirality because they are related to each other by a reflection: they are non-superimposable mirror images of each other.[2] Hands are chiral because there is no way to rotate the left hand so that it looks like the right hand.

In chemistry, stereoisomers are molecules that have the same molecular formula or atomic composition, but which are arranged differently in space.[3] One type of stereoisomer of particular interest to this Note is called an enantiomer. An enantiomer contains the same type and the same number of atoms as its mirror image and the atoms are all connected in the same order.[4] The only structural difference between one enantiomer and the other is the geometry of the spatial arrangement of the atoms. Again, visualize the left and right hands: four fingers, one thumb, a forehand, and backhand all with the same order of connectivity, but the thumbs point in opposite directions. In organic chemistry, enantiomeric pairs include compounds that have one or more stereogenic centers, or carbon atoms (C) with four different substituent atoms or groups of atoms.[5] These molecules

2. *See generally* JONATHAN CLAYDEN ET AL., ORGANIC CHEMISTRY 381-404 (2001).
3. *Id.* at 384.
4. *Id.* at 382.
5. *Id.* at 385.

are thus said to be chiral. For example, the enantiomers of the chemical compound bromochlorofluoromethane are displayed in Figure 1.



(*R*)-enantiomer (*S*)-enantiomer

Figure 1. The enantiomers of bromochlorofluoromethane are non-superimposable mirror images of each other; like left and right hands, they are "chiral." A solid wedge is used to indicate that the chlorine atom (Cl) is projecting out of the page, while a hashed line indicates that the fluorine atom (F) is behind the page.[6]

Chemists use various naming conventions to distinguish between different enantiomers of the same compound. If one enantiomer is labeled "(+)" or "(d)," then its counterpart is labeled "(–)" or "(l)."[7] A racemate, or racemic mixture, is an equal mixture of two enantiomers. Under these schemes, a racemate is labeled "(±)" or "(dl)." Another naming system labels biochemical molecules "(D)" or "(L)," although these are unrelated to the labels "(d)" and "(l)" described above. Yet another nomenclature system labels each stereogenic center "(R)" or "(S)" according to a set of rules.[8] Racemates are designated "(RS)" because they are comprised of both (R)-enantiomers and (S)-enantiomers.[9]

B. Biological Activities and Chiral Resolution

Purified enantiomers often exhibit very different biological activity. Just as a left hand does not fit into a right-handed glove, the (R)-enantiomer may not fit into the active site of an enzyme, whereas the (S)-enantiomer will, or vice-versa.[10] Consequently, one enantiomer may have a substantially different pharmacology and toxicology than the other

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6. *See also* Pfizer, Inc. v. Ranbaxy Labs. Ltd., 457 F.3d 1284, 1286 (Fed. Cir. 2006).

7. *Id.*; *see also* CLAYDEN, *supra* note 2, at 389.

8. (R) and (S)-descriptors, according to Cahn-Ingold-Prelog rules, will be used preferably herein when possible. *See* CLAYDEN, *supra* note 2, at 387.

9. *Id.*; *see also Pfizer*, 457 F.3d at 1286-87.

10. Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2 STAN. TECH. L. REV. 1, 3 (2007).

enantiomer.[11] Familiar examples include the compounds limonene, where the (R)-enantiomer is responsible for orange scent and the (S)-enantiomer is lemon scent, and ketamine, where the (S)-enantiomer is an anesthetic, but the (R)-enantiomer is a hallucinogen. The drug thalidomide is another well-known example: the (S)-enantiomer is a sedative that is effective against morning sickness, but the (R)-enantiomer causes birth defects.

When these types of compounds are produced in a laboratory under normal conditions, the racemic mixture obtained is comprised of 50% (R) and 50% (S).[12] Because of the different activity of each enantiomer, it is important to separate a racemic mixture into its constituents and to evaluate the properties of each one.[13] This very difficult separation process is called chiral resolution and is technically challenging because enantiomers have the same chemical properties, but not necessarily the same pharmacological properties. Consequently, traditional separation methods such as fractional distillation or chromatography may not work.[14] There is no way of predicting the properties of one enantiomer versus the other without resolving them from the racemate and testing each individually.[15] In recent decades, there has also been significant research and development toward generating new methodologies for the synthesis of one or the other enantiomer in excess, with an aim to preclude the need for resolution.[16]

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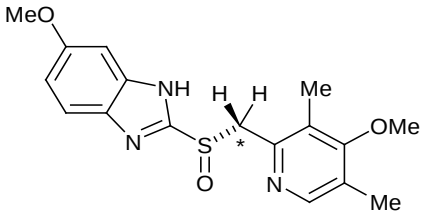
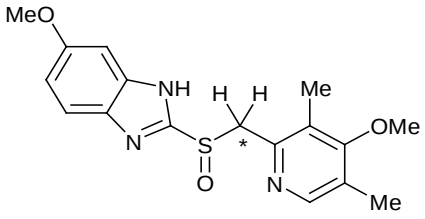
11. *Id.*
12. *See* CLAYDEN, *supra* note 2, at 399-404.
13. *Id.*
14. *Id.*
15. *Id.*
16. *See generally* Stephen G. Davies et al., *Oxazinanones as chiral auxiliaries: synthesis and evaluation in enolate alkylations and aldol reactions*, 4 ORGANIC & BIOMOLECULAR CHEMISTRY 2753 (2006); Stephen G. Davies et al., *Kinetic resolution and parallel kinetic resolution of methyl (RS)-5-alkyl-cyclopentene-1-carboxylates for the asymmetric synthesis of 5-alkyl-cispentacin derivatives*, 3 ORGANIC & BIOMOLECULAR CHEMISTRY 2762 (2005); Stephen G. Davies et al., *Double asymmetric induction as a mechanistic probe: conjugate addition for the asymmetric synthesis of a pseudotripeptide*, 9 CHEMICAL COMM. 1128 (2004); Stephen G. Davies et al., *Parallel kinetic resolution of* tert*-butyl (RS)-3-alkyl-cyclopentene-1-carboxylates for the asymmetric synthesis of 3-alkyl-cispentacin derivatives*, 2 ORGANIC & BIOMOLECULAR CHEMISTRY 3355 (2004); Stephen G. Davies et al., *Preparation of methyl (1R,2S,5S)- and (1S,2R,5R)-2-amino-5-*tert*-butyl-cyclopentane-1-carboxylates by parallel kinetic resolution of methyl (RS)-5-*tert*-butyl-cyclopentene-1-carboxylate*, 19 CHEMICAL COMM. 2410 (2003).

C. Enantiomeric Pharmaceuticals

Many chiral drugs were initially sold in racemic form because of the difficulty in separating the enantiomers from one another.[17] Single enantiomers can present significant advantages in potency, efficacy, and safety over the corresponding racemate, but this varies by case and is not a general rule.[18] Nevertheless, in recent years, as patents covering the racemic drugs began to expire, pharmaceutical companies started marketing the single-enantiomer versions of their drugs in order to extend product life and market monopoly.[19] This strategy is known as a "chiral switch," and is best exemplified by AstraZeneca's "purple pill" omeprezole (Figure 2).[20] The company saved their market share from erosion by generic competitors by selling the gastrointestinal drug as the single (S)-enantiomer Nexium® before the patent covering the (RS)-racemate Prilosec® expired.[21]



(S)-enantiomer
Nexium



(RS)-racemate
Prilosec

Figure 2. The purple pill chiral switch: Nexium® (left) is the (S)-enantiomer of the (RS)-racemate Prilosec® (right), but is it nonobvious? The stereogenic center is indicated by an asterisk.

Chiral molecules are big business for the pharmaceutical industry. Five of the six top-selling drugs worldwide in 2007 are all single enantiomers: Lipitor®, Advair®, Plavix®, Nexium®, and Diovan®.[22] Accordingly, this

17. Darrow, *supra* note 10, at 3.

18. Chris P. Miller & John W. Ullrich, *A Consideration of the Patentability of Enantiomers in the Pharmaceutical Industry in the United States*, 20 CHIRALITY 762, 762 (2008).

19. *See generally* A. Maureen Rouhi, *Chirality at Work: Drug Developers Can Learn Much from Recent Successful and Failed Chiral Switches*, CHEMICAL & ENGINEERING NEWS, May 5, 2003, at 56-61.

20. *Id.*

21. *Id.*

22. Top Ten Best-selling Drugs Worldwide 2007 (Nov. 15, 2008), http://qsarcenter.com/?p=9.

new trend of developing single-enantiomer therapeutics versus racemates, or introducing a single-enantiomer medicament to the market following the development and commercialization of a racemic mixture, has focused serious attention on the patentability of drug enantiomers.[23]

II. NOVELTY AND NONOBVIOUSNESS IN CHEMISTRY

Section II.A addresses the doctrine of novelty related to enantiomers, which is a relatively settled area of law. The nonobviousness of enantiomers is then analyzed in Section II.B as first considered in pre-*KSR* case law, focusing on the touchstone of structural similarity and the requirements related to motivation.

A. The Novelty of Enantiomers

Is an enantiomer novel where the racemate is known or disclosed in the art? With respect to novelty under 35 U.S.C. § 102, the issue of enantiomer patentability is whether a claim to a genus anticipates a claim to a species of that genus, where the racemate is a genus and the enantiomer is the species.[24]

A genus does not always anticipate a species within that genus.[25] Indeed, the effect of the disclosure of a genus on the patentability of a species depends on the size of the genus and the disclosure of any preferred sub-genera or species. A chiral molecule with only one stereogenic center gives rise to only two enantiomers. However, many chiral molecules have more than one stereogenic center, resulting in 2^n possible structural formulas, where n is the number of stereogenic centers. For example, as depicted in Figure 3, the racemic structure of atorvastatin (right) has two stereogenic centers, which gives rise to four ($2^2 = 4$) possible species. Pfizer's blockbuster drug Lipitor®—the biggest selling single-enantiomer drug in the world—is the (R,R)-species of this atorvastatin genus.[26]

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23. Miller & Ullrich, *supra* note 18, at 1 ("In 2003, not a single drug was brought into the US market as a racemic. . . mixture and 2004 saw the introduction of only one racemate . . . .").

24. *See* 35 U.S.C. § 102 (2006).

25. *See* Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1262 (Fed. Cir. 1989); *see also In re* Meyer, 599 F.2d 1026, 1031 (C.C.P.A. 1979) (finding that prior art genus did not "identically disclose or describe, within the meaning of *§ 102*" the claimed species "since the genus would include an untold number of species").

26. *See* Top Ten Bestselling Drugs Worldwide, *supra* note 22.

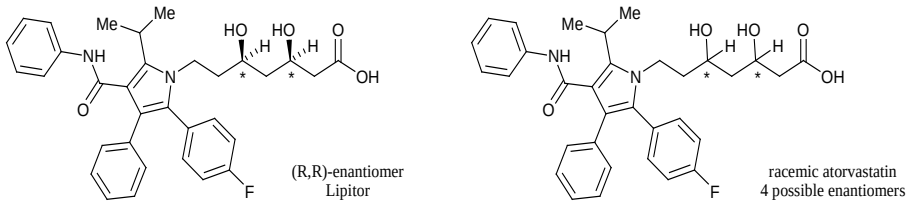

Figure 3. The top-selling drug in the world: Lipitor® (left) is the specific (R,R)-enantiomer within a genus of four possible isomers based on the structure of racemic atorvastatin (right). The stereogenic centers are indicated by astericks.

A genus of sufficiently limited and defined substituents may anticipate its species.[27] Put more plainly, a genus will anticipate a species within that genus that is not otherwise expressly disclosed if one of ordinary skill would immediately envisage the claimed compound from the disclosed genus.[28]

The patentability of a single enantiomer was first addressed by a court in *In re Williams*.[29] In that case, the Board of Patent Appeals and Interferences rejected a claim to a single-enantiomer compound both for lack of novelty and for obviousness.[30] The novelty rejection was based on a prior art reference that disclosed the production of a racemic compound with an identical formula to the claimed compound, although the reference did not indicate that it was racemic.[31] The Board of Patent Appeals held that the enantiomer could not be novel because it necessarily existed as part of the disclosed racemate.[32] The Court of Customs and Patent Appeals reversed, holding that "[t]he existence of a compound as an ingredient of another substance does not negative novelty in a claim to the pure compound, al-

27. *See In re* Schaumann, 572 F.2d 312, 316-17 (C.C.P.A. 1978) (finding that prior art disclosure embraces such a limited number of compounds closely related to one another in structure that it "provides a description of those compounds just as surely as if they were identified in the reference by name"); *In re* Petering, 301 F.2d 676, 682 (C.C.P.A. 1962) (finding that a genus of 20 compounds describes each species within the meaning of § 102(b)).

28. *Schaumann*, 572 F.2d at 316-17; *Petering*, 301 F.2d at 682.

29. 80 U.S.P.Q. (BNA) 150 (C.C.P.A. 1948). Note that the Court of Customs and Patent Appeals (C.C.P.A.) was the predecessor to the Court of Appeals for the Federal Circuit.

30. *Id.* at 151.

31. *Id.*

32. *Id.*

though it may, of course, render the claim unpatentable for [obviousness]."[33]

The rule from *In re Williams* that an enantiomer is not necessarily unpatentable over its previously disclosed racemate has since been applied consistently,[34] although it has produced some interesting results. For example, U.S. Patent No. 5,114,714 claims that using the (R)-enantiomers of the anesthetics isoflurane and desflurane is better than using the racemate, and U.S. Patent No. 5,114,715 claims that using the (S)-enantiomers of the same anesthetics is better than using the racemate. The patents are worded almost identically, except for the (R) and (S) descriptors.[35]

B. The Nonobviousness of Enantiomers

The question of whether an enantiomer is nonobvious in light of its disclosed racemate is far more difficult to answer. Compared to the novelty requirement, nonobviousness is a much bigger hurdle toward patentability, especially for enantiomers.

> A patent may not be obtained . . . 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 . . . .[36]

The analytical framework for an obviousness inquiry was set forth in *Graham v. John Deere Co.* and proceeds with the following steps: (1) determine the scope and content of the prior art; (2) ascertain the differences between the claimed invention and the prior art; (3) assess the level of ordinary skill in the art; and (4) evaluate evidence of secondary considerations, such as commercial success, long felt but unresolved need, and the failure of others, which are all sometimes called indicia of nonobvious-

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33. *Id.*

34. *In re* May, 574 F.2d 1082, 1090 (C.C.P.A. 1978) ("The novelty of an [enantiomer] is not negated by the prior art disclosure of its racemate."); Pfizer, Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495, 519 (D. Del. 2005) ("[C]ourts considering issues related to racemates and their individual isomers have concluded that a prior art disclosure of a racemate does not anticipate the individual isomers of the racemate. . . ."); Brenner v. Ladd, 247 F. Supp. 51, 56 (D.D.C. 1965) ("[I]t should be noted that plaintiffs' [enantiomer] is not considered by this court to be anticipated by the solution of [the racemate] disclosed in [the prior art]."); Sterling Drug Inc. v. Watson, 135 F. Supp. 173, 176 (D.D.C. 1955) ("[I]t matters not that [the enantiomer] in some form in combination may exist in nature, if it cannot be reduced to a form in which it can be used. It is this product which has been so reduced or resolved that it can be used that is here claimed.").

35. *See* Rouhi, *supra* note 19.

36. 35 U.S.C. § 103(a) (2006).

ness.[37] Even though the case dealt with a mechanical invention, these *Graham* factors apply regardless of the art in question.[38]

With respect to the second *Graham* factor, the Federal Circuit reiterated in *Eisai Co. v. Dr. Reddy's Laboratories* that structural similarity is the touchstone of the nonobviousness inquiry for patents claiming a novel chemical compound.[39] Under this scheme, a compound in the prior art is identified as a starting reference point and then an assertion of obviousness must be demonstrated based on how similar in structure a compound at issue is to that prior art disclosure, along with some motivation for having selected the known compound and then modifying it to achieve the claimed compound.[40] For example, consider Prilosec® and Nexium® as described above[41] and depicted in Figure 2. One might easily make the case that the chiral drug Nexium®, which is the (S)-enantiomer, is prima facie obvious in view of the racemic mixture Prilosec®. The single (S)-enantiomer is 50% of the racemic mixture because there is only one stereogenic center. The racemate Prilosec® is the logical starting reference point in an analysis of structural similarity because the two drugs have the same connectivity by definition; Nexium® is only differentiated from Prilosec® by the three-dimensional arrangement of the atoms around the stereogenic center. Thus, the critical prong of the obviousness test for chiral drugs concerns the motivation to arrive at the single-enantiomer compound.

Although the motivation to modify the prior art could come from many different fields, some teaching, suggestion, or motivation (TSM) was needed in a formal pre-*KSR* analysis.[42] In chemical cases, this motivation may be proved by showing a "sufficiently close relationship" between the prior art and the claimed compound that would "create an expectation . . . that the [new compound] would have similar properties [to the old]."[43]

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37. 383 U.S. 1, 17-18 (1966); s*ee also* Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986) (requiring that secondary considerations be considered before making an obviousness determination).

38. *See* KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1739 (2007) (reaffirming the *Graham* framework).

39. Eisai Co. v. Dr. Reddy's Labs., 533 F.3d 1353, 1356-57 (Fed. Cir. 2008). Although a post-*KSR* decision, *Eisai* offers a good review of the tests at issue.

40. *Id.* at 1357.

41. *See supra* text accompanying note 21.

42. See Rebecca S. Eisenberg, *Pharma's Nonobviousness Problem*, 12 LEWIS & CLARK L. REV. 375, 395-413 (2007), for a thorough review examining the development of case law in chemical obviousness from flexibility to rigid formalism pre-*KSR*. *See also KSR*, 127 S. Ct. at 1734.

43. *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990).

In other words, an obvious substitution would have to be predictable.[44] The unpredictable nature of the chemical arts thus allows an assertion of similarity to be rebutted by a sufficient demonstration of nonobviousness that employs secondary considerations or objective indicia. Indeed, one of the most important secondary considerations is evidence of unexpected or superior results. Such results may prove that the enantiomer refutes the normal expectation that a compound with similar structure will have similar properties.

Before *KSR*, the courts held that mere knowledge of a previously disclosed racemic mixture, such as the drug Prilosec®, did not provide adequate motivation to prompt one of ordinary skill in the art to resolve the racemate to its constituent enantiomers.[45] Absent any teaching or suggestion in the prior art to derive the single-enantiomer, the chiral drug Nexium® would likely have been held nonobvious over Prilosec®. Indeed, a district court in one pre-*KSR* case found that no motivation existed in the prior art to resolve racemic atorvastatin into its constituent enantiomers as late as 1991, and thus the (R,R)-enantiomer of atorvastatin—the chiral drug Lipitor®—was held nonobvious over the racemate.[46]

The case in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*[47] addressed the alleged invalidity of a patent covering the antibiotic Levaquin® and presented a very different, now more common, set of facts. The active pharmaceutical ingredient in Levaquin® is levofloxacin, which is the (S)-enantiomer of the racemic antibiotic ofloxacin (Floxin®).[48] Mylan challenged the patented claims to the single-enantiomer levofloxacin as obvious in view of prior art that both disclosed the racemate and, as early as the mid-1980s, provided "ample motivation to separate the optical isomers" of the racemate.[49] Patent holder Ortho-McNeil provided evidence of unexpected results that showed that the single-enantiomer levofloxacin is approximately ten times more soluble than the racemic mixture.[50] The court noted that, prior to the discovery of levofloxacin, the largest reported difference in solubility between an enantiomer and its racemate was only fivefold.[51] The court indicated that this difference alone

44. Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008) ("[E]asily traversed, small and finite number of alternatives. . . might support an inference of obviousness.").

45. Pfizer Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495, 517 (D. Del. 2005).

46. *Id.*

47. 348 F. Supp. 2d 713 (N.D.W. Va. 2004).

48. *Id.* at 721.

49. *Id.* at 752. Enantiomers are also called optical isomers.

50. *Id.* at 755.

51. *Id.*

was an unexpected result and presumably sufficient by itself to rebut the prima facie case of obviousness, but nonetheless further noted that the single-enantiomer is approximately two times more potent than the racemate.[52] While the greater potency alone might not have been persuasive,[53] the court was persuaded by a showing that the (S)-enantiomer is less toxic than the racemate, which appeared to contradict the conventional scientific wisdom in the art.[54] Thus, taken altogether, the district court found that the unexpected and superior results put forth for the single-enantiomer levofloxacin were sufficient to overcome a prima facie challenge of obviousness in view of the racemate and the motivation to resolve it.[55] Accordingly, the district court upheld the validity of the patent claims.[56] The Federal Circuit affirmed without written opinion.[57]

Although the Lipitor® and Levaquin® cases reached the same result, holding the respective single-enantiomer drugs nonobvious, the difference in the application of the motivation element between them underscores that obviousness is a fact-specific inquiry.[58] Nevertheless, the patent bar and commentators expected that, in the absence of any rigid TSM requirement post-*KSR*, it would be easier to invalidate patent claims as obvious or for the U.S. Patent and Trademark Office to deny patent protection.[59] It is known that enantiomers exhibit different activities[60] and it has been described in the literature that companies actively engage in the practice of separating racemic mixtures in order to determine which compo-

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52. *Id.*

53. The court reasoned that resolution into component enantiomers could at best be expected to yield a two-fold increase in activity: presumably, the two-fold limit is imposed by the fact that if even 100% of the activity level results from only one enantiomer, and the other is completely inactive, then removing the inactive enantiomer will simply have the effect of doubling the activity level per unit of compound remaining; if both enantiomers are somewhat active, then removing the less active one would increase the activity level by something less than 100%.

54. *Ortho-McNeil*, 348 F. Supp. 2d at 755.

55. *Id.* at 755, 760.

56. *Id*.

57. Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 161 F. App'x 944 (Fed. Cir. 2005).

58. Recall that the court in *Pfizer*, in considering Lipitor®, found that there was no motivation to resolve the racemate. Pfizer Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495, 517 (D. Del. 2005). The court in *Ortho-McNeil*, in considering Levaquin®, found that "ample motivation" to resolve the racemate was overcome by unexpected results. *Ortho-McNeil*, 348 F. Supp. 2d at 752.

59. Calvert D. Crary, *Impact of* KSR v. Teleflex *on Pharmaceutical Industry*, LITIG. NOTES, May 2, 2007, at 1.

60. *See supra* text accompanying note 10.

nent to market.[61] It follows that an ordinarily skilled artisan may generally be considered to be aware of the benefits of chiral drugs and the techniques to develop them. Even before *KSR*, the Federal Circuit indicated that such common knowledge can be a source of motivation to combine references.[62] Thus, a looming question for pharmaceutical companies has been how the *KSR* decision will impact chemical patents.

III. POST-*KSR* OBVIOUSNESS OF ENANTIOMERS

A. Lessons from *KSR*

One of the major shifts resulting from *KSR* concerned the type of evidence that can be marshaled to support a finding of obviousness.[63] The Supreme Court rejected the rigid application of the TSM test for patent obviousness, but did not abolish it.[64] Chiral drugs are desirable and broad general knowledge of traditional technologies for isolating single-enantiomers from racemic mixtures exists.[65] As knowledge of enantiomers continues to increase and techniques for chiral resolution continue to improve, less innovation will be required to make a single enantiomer from its racemate, and thus prospective inventors will have more motivation to pursue that aim. Yet, to be obvious under § 103, there must still be some articulated reason why a person of ordinary skill in the art would combine the prior art elements to arrive at the claimed invention.[66] Critically, secondary considerations are still significant evidence to rebut a prima facie case of obviousness.[67]

The Supreme Court was careful to note that *KSR* simply mandated flexibility and reminded courts that the requisite motivation for the invention need not originate from the words of written references, but can arise instead from the application of common sense to an apparent market need.[68] This would seemingly spell trouble for the nonobviousness of pharmaceutical patents directed toward single-enantiomer drugs. Yet, in response, the Federal Circuit has seemingly established a framework for

61. *See* Rouhi, *supra* note 19.

62. *In re* Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

63. *See* Justin Lee, Note, *How* KSR *Broadens (Without Lowering) the Evidentiary Standard of Nonobviousness*, 23 BERKELEY TECH. L.J. 15, 15 (2008).

64. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007).

65. *See* CLAYDEN, *supra* note 2, at 399-404.

66. *See* Letter from Margaret A. Facarino, Deputy Comm'r for Patent Operations, U.S. Patent & Trademark Office, to Tech. Ctr. Dirs., U.S. Patent & Trademark Office (May 3, 2007) (on file with the U.S. Patent and Trademark Office).

67. *Id.*

68. *KSR*, 127 S. Ct. at 1742.

assessing nonobviousness of enantiomeric pharmaceutical products based on the unpredictability of their properties and success in the separation process itself, which does not mark a substantive departure from pre-*KSR* jurisprudence.

B. Analysis of Post-*KSR* Cases

1. Enantiomer Found Obvious—Patent Claims Invalid

Aventis Pharma Deutschland GmbH v. Lupin, Ltd.[69] is instructive as a pre-*KSR* trial court case reviewed by the Federal Circuit post-*KSR*. The district court held valid patent claims to a single-enantiomer of the hypertension drug ramipril (Altace®) with five (S)-configured stereogenic centers.[70] The Federal Circuit reversed, holding the claims invalid as obvious in light of the prior art disclosure of a mixture of just two of the thirty-two possible isomers.[71]

On the question of nonobviousness, the Federal Circuit first noted that the district court had found that Lupin had "failed to meet its burden of proof . . . that a person of skill in the art would have been motivated to purify 5(S) ramipril into a composition substantially free of other isomers."[72] However, the Federal Circuit further noted that since the district court's decision, the *KSR* opinion counseled that it would be sufficient to show that the claimed compound and the prior art compounds are closely enough related so as to create an expectation that the new compound would have similar properties to the old one.[73] In this case, the record showed that the inventor understood that the 5(S)-enantiomer was the therapeutically active ingredient in the mixture.[74] Nevertheless, a purified form of a mixture that existed in the prior art is not always prima facie obvious over the mixture.[75]

The *Aventis* court held that no explicit teaching to purify or to concentrate a particular ingredient that is known to impart desirable properties on a mixture is required to sustain a finding of obviousness.[76] If a person of ordinary skill in the art has reason to believe that the particular constituent has special benefits, then the purified compound is prima facie obvious

69. 499 F.3d 1293 (Fed. Cir. 2007).
70. *Id.* at 1294.
71. *Id.* at 1295.
72. *Id.* at 1300.
73. *Id.* at 1301.
74. *Id.*
75. *Id.*
76. *Id.*

over the mixture.[77] Thus, the Federal Circuit found that in this case the "the prior art provides a sufficient reason to look to the 5(S) configuration" and noted that "Aventis's protestations notwithstanding, there is no evidence that separating the 5(S) and (SSSSR) ramipril [mixture] was outside the capability of an ordinarily skilled artisan."[78]

Aventis attempted to rebut the prima facie finding of obviousness by arguing that the purified 5(S)-ramipril exhibited unexpected increased potency when compared with the next most potent isomer, the (RRSSS) isomer.[79] However, the court was not persuaded, finding instead that Aventis was making the wrong comparison: "Aventis must show that the 5(S) ramipril had unexpected results not over all of its stereoisomers, but over the mixture [of 5(S) and (SSSSR)], which did not contain the (RRSSS) form."[80] Failing such a demonstration, Aventis could not rebut the prima facie case. Owing to this lack of any real evidence of secondary indicia of nonobviousness in light of the prior art teaching of a mixture of two enantiomers already isolated from the thirty-two possible based on the racemate, it is unlikely that this result would have been different even if the appeal was heard pre-*KSR*.

The court also distinguished the *Aventis* case from *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*,[81] which had been decided one week earlier, and where the prima facie case of obviousness was rebutted because the particular enantiomer at issue showed unexpected benefits and evidence indicated that the racemic mixture would have been difficult for a person of ordinary skill in the art to separate.[82]

2. Enantiomers Found Nonobvious—Patent Claims Valid

Forest Labs is an important case in the "new" understanding of obviousness. Interestingly, in its multi-page discussion of nonobviousness, the appellate panel did not mention *KSR* even though the Supreme Court had decided it almost half a year earlier. Forest held an expired patent on a racemic form of the selective serotonin reuptake inhibitor citalopram.[83] After considerable effort, Forest's scientists doubled the strength of the drug by isolating the (+)-stereoisomer—which turned out to be the only

77. *Id.*
78. *Id.* at 1302.
79. *Id.*
80. *Id.*
81. 501 F.3d 1263 (Fed. Cir. 2007).
82. *Id.* at 1269.
83. *Id.* at 1266.

active isomer—and patented that isomer in a "substantially pure" form.[84] A prior art pharmacologic paper had suggested that the (–)-enantiomer would be the potent isomer, but the reference did not describe the preparation of the enantiomer.[85] Thus, while the prior art reference did suggest isolation of a stereoisomer to create a more potent drug, it did not enable the process of isolation.[86] As the *Ortho-McNeil* court had done in the face of ample prior art motivation to resolve the racemate in the pre-*KSR* Levaquin® decision,[87] the *Forest* court considered the totality of circumstances in concluding that the chiral drug was nonobvious.[88] Specifically, the *Forest* court focused on secondary indicia such as the difficulty in isolating the stereoisomer without undue experimentation, the unexpected results of the single-enantiomer product, and commercial success.[89]

This principle that a prima facie case of obviousness for chiral drugs is still rebuttable post-*KSR* by demonstrating objective indicia of nonobviousness was again addressed recently in *Sanofi-Synthelabo v. Apotex, Inc*.[90] In that case, the Federal Circuit upheld a district court ruling that the patent claims to the (d)-enantiomer of clopidogrel bisulfate—marketed as Plavix® for preventing heart attacks and strokes by reducing platelet aggregation—were not obvious in view of the prior art racemate.[91] The court reasoned that that an earlier patent covering the racemate did not disclose to a skilled artisan how the enantiomers of the racemate could be separated.[92] The evidence showed that the patentee had expended a considerable amount of time and effort trying to resolve the enantiomers.[93] Furthermore, the (d)-enantiomer (Plavix®) exhibited good platelet inhibition, whereas the (l)-enantiomer was completely ineffective, and this difference in biological properties was unexpected in light of the prior art.[94] The toxicity also differed: the (l)-enantiomer was significantly more lethal than the (d)-enantiomer, and the (l)-enantiomer was neurotoxic while the (d)-

84. *Id.* at 1268.
85. *Id.*
86. *Id.* at 1268-69.
87. Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (N.D.W. Va. 2004), *aff'd* 161 F. App'x 944 (Fed. Cir. 2005).
88. *Forest*, 501 F.3d at 1269.
89. *Id.*
90. 550 F.3d 1075 (Fed. Cir. 2008).
91. *Id.*
92. *Id.* at 1088.
93. *Id.* at 1081, 1088.
94. *Id.* at 1081 ("The experts for both sides agreed that while it was generally known that enantiomers can exhibit different biological activity, this degree and kind of stereoselectivity is rare, and could not have been predicted.").

enantiomer was not.[95] Thus, the patent was held nonobvious because the properties of the enantiomer were truly unexpected.

The *Sanofi* court purported to assess the so-called unexpected properties of the enantiomer product at issue on a spectrum between the facts presented in *Forest* and those in *Aventis*.[96] In *Forest*, the court had affirmed that the (+)-enantiomer of citalopram would not have been obvious in light of the known racemate because it was demonstrated that the therapeutic properties of the (+)-enantiomer were unexpected, along with other secondary considerations.[97] In contrast, the *Aventis* court held that the potency of the ramipril isomer was precisely as expected compared to the mixture.[98] The *Sanofi* court thus concluded that the evidence of unexpected properties and the totality of secondary indicia were closer to *Forest* (à la *Ortho-McNeil*) than to *Aventis*.[99] Accordingly, between the facts of these two post-*KSR* cases—*Aventis* and *Forest*—the Federal Circuit has established a framework for analyzing nonobviousness in single-enantiomer products. This scheme for evaluating the unexpected and unpredictable properties of the single-enantiomer products is similar to that followed pre-*KSR*, and the court further cautioned against hindsight bias and ex post reasoning in an obviousness determination concerning the separation of an enantiomer with desirable properties from a selected racemate.[100]

The *Sanofi* court explicitly rejected a number of arguments asserted by Apotex that one of ordinary skill in the art would have been motivated to separate the enantiomers from the racemic mixture.[101] The court found that, even though at the time of the invention the level of ordinary skill was such that there were many well-known processes for separating enantiomers, the level of difficulty experienced by the inventor was expository of the inherent unpredictability in this field and the unexpected results of the chiral drug product.[102] Additionally, knowledge that such separation was desirable and would lead to allocation of favorable properties in the

95. *Id.*

96. *Id.* at 1089.

97. Forest Labs., Inc. v. Ivax Pharms., Inc., 501 F.3d 1263, 1269 (Fed. Cir. 2007).

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

99. *Sanofi*, 550 F.3d at 1089.

100. *Id.* at 1088 ("The application of hindsight is inappropriate where the prior art does not suggest that [the] enantiomer could reasonably be expected to manifest the properties and advantages that were found. . .") (citing KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007); Graham v. John Deere Co., 383 U.S. 1, 36 (1996)).

101. *Id.* at 1087-88.

102. *Id.*

enantiomer components of the mixture was also not found to be persuasive enough motivation to be deemed obvious.[103] The court also rejected Apotex's argument that Sanofi only resolved the racemate in response to a market need for single-enantiomer products imposed by the possibility of future regulatory requirements to separate enantiomers.[104]

This growing body of post-*KSR* case law cautions practitioners to be proactive about documenting and preserving proof of the unpredictability of their work. The lesson of these cases is that if the separation process of chiral resolution itself is particularly difficult, and the properties of the resulting products are unpredictable, especially compared to the mixture, then the nonobviousness of the enantiomer is enhanced.

3. "Obvious-To-Try" Standard

The Supreme Court's decision in *KSR* did not discuss the patentability of enantiomers, but it did address the obvious-to-try test, which is implicated directly in evaluating the validity of claims covering a single enantiomer.[105] In discussing the test, the Court stated that if a finite number of identified, predictable solutions exist, then a person of ordinary skill in the art has good reason to pursue known options.[106] Some practitioners have thus asserted that:

> As applied to enantiomers, a finite number of identified solutions always exists—exactly two if there is a single [stereogenic] center, as in Plavix®. Moreover, it is always a known option to separate a racemate into its two enantiomers, especially where a process for doing so was disclosed in the prior art . . . design need or market pressure is indirectly supplied because it is generally known that a single enantiomer will be superior to the racemate in at least some respects. If the patent on the racemate will soon expire, market pressure to obtain a patent on an enantiomer may well exist—the 'chiral switch.'"[107]

The premise is that given enough time and resources, a person of ordinary skill would be able to try all possible prior art combinations, including the patented one.

This echoes Apotex's argument in *Sanofi* (1) that there were a discreet set of known enantiomer products that could potentially be isolated from

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103. *Id.*
104. *Id.* at 1089.
105. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007).
106. *Id.*
107. Brian D. Coggio & Steven N. Hird, *The Patentability of Drug Enantiomers*, N.J.L.J., Oct. 2007, at 2.

the disclosed racemic mixture, (2) that there were at least ten well-known techniques that were the state of the art at the time to affect a chiral resolution, and (3) that all that was required to arrive at the patented combination was experimentation.[108] However, the court rejected Apotex's argument based largely on evidence of the inventor's own failed attempts over five months testing thirty compositions with various acids at various concentrations in various solvents before finding one that yielded a result.[109] The language of *KSR* itself reiterated the pre-*KSR* obvious-to-try doctrine that one must have a reasonable expectation of success for a finding of obviousness.[110]

In addition to refining *KSR* in *Eisai*,[111] the Federal Circuit again recently emphasized the lack of predictability in the field of pharmaceutical chemistry by rejecting the obviousness attack on the active pharmaceutical ingredient in Takeda's anti-diabetic drug Actos®.[112] Enantiomer patents likely will survive obviousness challenges provided that (1) there was no understanding in the art that one enantiomer was expected to be more active than the other, and (2) no drug in the prior art, having similar chemistry, was shown to have differential activity. The *KSR* language will not render a single-enantiomer claim obvious because, although there will be only two "choices" for the skilled artisan to make when a compound has one stereogenic center, the question of whether the two enantiomers can be separated is not trivial, and there is no expectation either way of successfully showing differential activity. Unless the test of "it might work" is enough, these claims should remain valid under *KSR* in such an unpredictable area as the pharmaceutical arts.

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108. *Sanofi*, 550 F.3d at 1087-88.

109. *Id.* at 1088.

110. *KSR*, 127 S. Ct. at 1742.

111. Eisai Co. v. Dr. Reddy's Labs., 533 F.3d 1353, 1359 (Fed. Cir. 2008) (concluding that assumptions about the prior art landscape found in *KSR* often do not apply to cases concerning chemical compounds).

112. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., 492 F.3d 1350, 1359 (Fed. Cir. 2007) ("Thus, this case fails to present the type of situation contemplated by the [Supreme] Court when it stated that an invention may be deemed obvious if it was 'obvious to try.' The evidence showed that it was not obvious to try."); *see also* Andrew V. Trask, *"Obvious to Try": A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 FORDHAM L. REV. 2625, 2649-57 (2008) (advocating a rejection of the Federal Circuit's application of "obvious-to-try" for pharmaceutical inventions).

IV. CONCLUSIONS

Although a decrease in the number of new chiral switches is likely, it is just as likely that the pharmaceutical industry will continue to bring more single-enantiomer drugs to market in lieu of racemic mixtures. Accordingly, issues related to the patentability of enantiomers will be of ongoing interest. Enantiomers may also be the subject of patent claims to specific therapeutic indications or pharmaceutical formulations that are not disclosed or suggested by the art, presenting separate issues of patentability to which the principles discussed herein should still apply. In the past, the level of unpredictability in the pharmaceutical sciences has served as a firewall to protect chiral drug patents from being found obvious. This will likely not change in the foreseeable future, even as chiral resolution technologies give way to a next-generation focus on direct asymmetric synthesis. A critical lesson from post-*KSR* cases is that, in terms of rebutting charges of obviousness, evidence of experimental failures may be as important as proof of technological and commercial success.