



The Patentability of Enantiomers: Implications for the Pharmaceutical Industry

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INTRODUCTION

A. The Pharmaceutical Industry

¶1 When it comes to sales figures, Big Pharma certainly lives up to its reputation. A recent study estimates worldwide pharmaceutical sales exceed \$600 billion.¹ The United States is by far the single largest market for pharmaceutical products,² where companies invest hundreds of millions of dollars in drug discovery³ and boast annual sales of \$252 billion.⁴

¶2 What may come as more of a surprise is that a large portion of pharmaceutical sales is derived from a class of molecules called chiral molecules,⁵ which have unique qualities that make them particularly interesting from a legal standpoint. The importance of chiral drugs cannot be overstated. Worldwide sales of chiral drugs reached more than \$159 billion in 2002,⁶ a figure which is expected to increase to over \$200 billion by 2008.⁷ In fact, chiral molecules comprise more than half the drugs approved worldwide,⁸ including many of the world's top-selling drugs.⁹ For example, Lipitor® and Zocor® (the world's first and fifth top selling drugs in 2005)¹⁰ contain chiral molecules as the active pharmaceutical ingredient.¹¹ Other well-known chiral pharmaceuticals include ibuprofen, (sold under

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¹ Matthew Herper & Peter Kang, *The World's Ten Best-Selling Drugs*, FORBES.COM, Mar. 27, 2006, http://www.forbes.com/2006/03/21/pfizer-merck-amgen-cx_mh_pk_0321topdrugs.html. An estimate by the Organization for Economic Cooperation and Development places this figure in excess of \$450 billion. ORG. FOR ECON. COOPERATION AND DEV., DRUG SPENDING IN OECD COUNTRIES UP BY NEARLY A THIRD SINCE 1998, ACCORDING TO NEW OECD DATA (Aug. 6, 2005), available at http://www.oecd.org/document/25/0,2340,en_2649_201185_34967193_1_1_1_1,00.html.

² Selena Class, *Pharma Overview*, CHEM. & ENG'G NEWS, Dec. 2, 2002, at 39, 39.

³ Natalie A. Lissy, *Patentability of Chemical and Biotechnology Inventions: A Discrepancy in Standards*, 81 WASH. U. L.Q. 1069, 1069-70 (2003).

⁴ Herper & Kang, *supra* note 1.

⁵ Stephen C. Stinson, *Chiral Drugs*, CHEM. & ENG'G NEWS, Oct. 23, 2000, at 55, 55; Christopher J. Welch et al., *Preparative Chiral SFC as a Green Technology for Rapid Access to Enantiopurity in Pharmaceutical Process Research*, LC-GC EUROPE, May 2005, at 264, 264.

⁶ A. Maureen Rouhi, *Chiral Business*, CHEM. & ENG'G NEWS, May 5, 2003, at 45, 46.

⁷ Paul Moran, *New Ligands for Asymmetric Hydrogenation*, SPECIALTY CHEMS. MAGAZINE, July-Aug. 2003, at 16, 16.

⁸ John Caldwell, *Do Single Enantiomers Have Something Special to Offer?*, HUMAN PSYCHOPHARMACOLOGY, Dec. 2001, at S67, S67 (reporting that 949 of 1675 drugs listed in the *Pharmacopoeia* are chiral); *Chiral Drugs Show Signs of Maturity*, CHEM. BUS., Apr. 1998, at 31.

⁹ Welch et al., *supra* note 5, at 264.

¹⁰ Herper & Kang, *supra* note 1.

¹¹ Rouhi, *supra* note 6, at 46; *Pfizer Inc. v. Ranbaxy Labs.*, 405 F. Supp. 2d 495, 500 (D. Del. 2005) (describing Lipitor® as “the largest selling pharmaceutical in history”).

the brand name Motrin®, and as over-the-counter versions Advil® and Nuprin®),¹² Claritin®, Allegra®,¹³ Zolof®¹⁴, Paxil®,¹⁴ Aleve®,¹⁵ Prilosec® (and its racemic switch Nexium®), Prevacid®, Zyrtec®, Ritalin®, and even thalidomide.¹⁶

¶3 Like all inventions, the chiral compounds contained in pharmaceuticals must meet the statutory requirements of novelty, usefulness, and nonobviousness in order to be patentable.¹⁷ Compounds exhibiting desirable pharmacological activity will generally meet the usefulness requirement. However, because of the economic importance and unique structural characteristics of chiral molecules, challenges to their patentability on the bases of novelty and nonobviousness have been asserted since as early as 1948.¹⁸ With the explosive growth of the pharmaceutical industry—and particularly of chiral molecules¹⁹—over the last several decades, the patentability of chiral molecules has taken on increased significance²⁰ and remains a subject of litigation.²¹

¶4 This paper describes the legal framework surrounding the patentability of enantiomers (a subgroup of chiral molecules), identifies current questions and issues, and suggests how those issues should be resolved.

B. The Chemistry of Chiral Molecules

¶5 To understand the patentability of enantiomers, it is first necessary to understand their structure and characteristics. Chiral molecules exist in two distinct mirror image forms, called enantiomers.²² Enantiomers are thus often likened to the right and the left hands, which are mirror images of each other, but which can not be superimposed upon each other.²³ Each enantiomer is therefore distinct from its counterpart. At the same time, knowledge of the structure of one enantiomer necessarily suggests the structure of the other. This observation motivates a fundamental inquiry: If one enantiomer is disclosed in the prior art, will its corresponding mirror image be unpatentable as obvious under § 103?

¶6 An isomer is one of a number of molecules that have the same molecular formula, but differ in the way the atoms are arranged. An enantiomer is a special type of isomer, in that it contains the same type and number of atoms as its mirror image, but the atoms are all connected in the same order.²⁴ The only structural difference between one enantiomer and the other is the geometry of the spatial arrangement of the atoms (here again, it is helpful to visualize the left and right hands). Given

¹² *Chiral Drugs Show Signs of Maturity*, *supra* note 8, at 31.

¹³ Class, *supra* note 2, at 40.

¹⁴ *Do Single Stereoisomer Drugs Provide Value?*, THERAPEUTICS LETTER, June-Sept. 2002, available at <http://www.ti.ubc.ca/PDF/45.pdf>.

¹⁵ Michael Strong, *FDA Policy and Regulation of Stereoisomers: Paradigm Shift and the Future of Safer, More Effective Drugs*, 54 FOOD & DRUG L.J. 463, 470 (1999).

¹⁶ U.S. ADOPTED NAMES COUNCIL, GEOMETRIC ISOMERISM AND CHIRALITY: THE USAN PERSPECTIVE, available at <http://www.ama-assn.org/ama/pub/category/15698.html> (last visited Mar. 27, 2006). Thalidomide, infamous due to the birth defects that resulted after the drug was sold in the European market, is a special case because the two enantiomers interconvert at biologic pH. Although only one enantiomer is responsible for the birth defects, this interconvertibility makes safe administration of the drug a challenge.

¹⁷ 35 U.S.C. §§ 101-103 (2006).

¹⁸ *In re Williams*, 171 F.2d 319 (C.C.P.A. 1948).

¹⁹ Welch et al., *supra* note 5, at 264.

²⁰ Caldwell, *supra* note 8, at S69-S70 (arguing that when considering a chiral switch, “patent protection must be available for the single enantiomer”). A.J. Hutt & J. Valentová, *The Chiral Switch: The Development of Single Enantiomer Drugs from Racemates*, ACTA FACULTATIS PHARMACEUTICAE UNIVERSITATIS COMENIANAE, 2003, at 7 (“Over the last ten to fifteen years drug chirality, particularly the use of single enantiomers . . . has become an area of considerable interest.”). Furthermore, the pharmaceutical industry is not the only one where single enantiomers are significant. The production of chiral compounds as single enantiomers is also a topic of ever-increasing importance in the chemicals industry. Kazuya Okano & Makoto Ueda, *Asymmetric Reduction Using Biocatalytic Reactions*, SPECIALTY CHEMS. MAGAZINE, Dec. 2004, at 40.

²¹ See, e.g., *Pfizer Inc. v. Ranbaxy Labs.*, 405 F. Supp. 2d 495 (D. Del. 2005) (Lipitor®); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713 (N.D. W. Va. 2004) (Levaquin®).

²² JOHN MCMURRY, ORGANIC CHEMISTRY 287 (3d ed. 1992). Enantiomers are sometimes referred to as “optical isomers.”

²³ See, e.g., *Ortho-McNeil*, 348 F. Supp. 2d at 720.

²⁴ *Ranbaxy*, 405 F. Supp. 2d at 502.

such a high level of similarity and predictability of structure, is an enantiomer even novel under § 102 if its mirror image has previously been disclosed?

¶17 These questions might appear to be purely academic, but nothing could be further from the truth. Although purified enantiomers exhibit identical physical and chemical properties (such as boiling point, density, and chemical reactivity) to their corresponding mirror images, they frequently exhibit very different biological activity.²⁵ This is because, just like a left-handed person who cannot use a right-handed baseball glove, one enantiomer may not fit into the active site of an enzyme where the other will. This means one enantiomer may have substantially different pharmacology and toxicology than the other enantiomer.²⁶ It also means pharmaceutical companies may want to market a drug containing only the more active enantiomer,²⁷ even if its mirror image has been disclosed or even previously patented. For a blockbuster drug based on a single enantiomer, the ability or inability to acquire a patent can significantly affect profitability by blocking the entrance of generic competitors.²⁸

¶18 The differing activity of enantiomers has long been recognized in the pharmaceutical industry,²⁹ and by 1998 an entire generation of single-enantiomer drugs was already coming off patent.³⁰ Around the same time, it was predicted that single-enantiomer drugs would become the standard within the pharmaceutical industry.³¹ This prediction is coming to pass. Lipitor® and Zocor®, mentioned above, are not only chiral, but are both single-enantiomer drugs.³² Furthermore, a survey of 1200 drugs under development worldwide disclosed that 820 were chiral and, of those, 610 were being developed as single enantiomers.³³ The distinction between different enantiomers is so important that the Food and Drug Administration has issued a policy statement calling for single-enantiomer data during the approval process.³⁴

¶19 Up to this point, the relevant inquiry has been framed in terms of the patentability of one enantiomer over its mirror image. In practice this is not usually the question presented. This is because when chiral molecules are synthesized in the laboratory—for example, in the preparation of pharmaceuticals—the two mirror image enantiomers are created in a fifty-fifty ratio called a racemic mixture, or racemate.³⁵ Due to the difficulty in separating the enantiomers from one another, many chiral drugs were initially sold in racemic form. As the patents covering these racemates expire, pharmaceutical companies naturally look to marketing the single-enantiomer versions of the drugs in order to extend product life and their market monopoly.³⁶ The question thus normally becomes not

²⁵ FOOD AND DRUG ADMIN., FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS (1992), available at <http://www.fda.gov/cder/guidance/stereo.htm>; see also Caldwell, *supra* note 8, at S67 (noting that different stereoisomers have been reported to have different tastes and odors); GEOMETRIC ISOMERISM AND CHIRALITY: THE USAN PERSPECTIVE, *supra* note 16.

²⁶ Policy on Period of Marketing Exclusivity for Newly Approved Drug Products with Enantiomer Active Ingredients, 62 Fed. Reg. 2167 (Jan. 15, 1997).

²⁷ Strong, *supra* note 15, at 477 (“[E]ven though approximately 120 drugs currently in Phase III trials are racemates, most chiral compounds now in preclinical development are single enantiomers.”).

²⁸ Hutt & Valentová, *supra* note 20, at 15.

²⁹ Caldwell, *supra* note 8, at S67 (reporting enantiomer studies from 1904 and 1908); Peter Mansfield et al., *Single-Enantiomer Drugs: Elegant Science, Disappointing Effects*, CLINICAL PHARMACOKINETICS, 2004, at 287, 287 (“Drug chirality has been researched . . . since . . . 1874.”).

³⁰ *Chiral Drugs Show Signs of Maturity*, *supra* note 8, at 31.

³¹ Patricia Van Arnum, *Chirals Spiral Upward*, CHEM. MARKETING REPORTER, Aug. 5, 1996, at SR27.

³² Rouhi, *supra* note 6, at 46.

³³ *Chiral Drugs Show Signs of Maturity*, *supra* note 8, at 31.

³⁴ FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS, *supra* note 25; *Exciting Times Ahead for Chiral Technology*, LABORATORYTALK.COM, June 18, 2003, <http://www.laboratorytalk.com/news/fro/fro160.html>.

³⁵ Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713 (N.D. W. Va. 2004). In contrast, naturally occurring compounds are often single enantiomers. Although the terms “racemic mixture” and “racemate” are frequently used interchangeably in the literature, they are not identical. For a discussion of terminology, see Alan G. Mitchell, *Racemic Drugs: Racemic Mixture, Racemic Compound, or Pseudoracemate?*, J. PHARMACY PHARM. SCI., Jan.-Apr. 1998, at 8.

³⁶ Stephen C. Stinson, *Chiral Pharmaceuticals*, CHEM. & ENG'G NEWS, Oct. 1, 2001, at 79. This practice has been referred to as a “line extension” chiral switch. Caldwell, *supra* note 8, at S70.

whether one enantiomer is patentable over its previously disclosed mirror image enantiomer, but whether the enantiomer is patentable over its previously disclosed racemate.

¶10 In addition to composition claims, United States patent law also provides for the patenting of processes.³⁷ As alluded to earlier, separating or “resolving” a racemate into its component parts is technically challenging. This is because each enantiomer has the same chemical (but not necessarily pharmacological) properties, and therefore traditional separation methods such as fractional distillation or chromatography may not work. Where the enantiomer as a composition is held to be nonpatentable over its racemate, would a new, useful, and nonobvious process for resolving the racemate be patentable? Even if the process is patentable, such a patent would not provide the right to exclude others from making and selling the product produced by that process. This is because there may be other, noninfringing processes that are capable of creating the same product. So perhaps a more important question is: If a racemate was disclosed long ago in the prior art, but a process to resolve the enantiomers has only recently been developed, can the enantiomer (as a compound) still be patented?

¶11 Many other questions remain as well. What if the same process has been used successfully on other racemates, but not on the one in question? Is it then obvious to combine the known racemate with the known resolution process? If so, does this mean that as more and more processes are developed and used on more and more racemates, it will become increasingly difficult to obtain patent protection for single-enantiomer drugs? In addition, many chiral molecules have more than one stereogenic center, resulting in not just two enantiomers, but in 2^{n-1} pairs of enantiomers (where n is the number of stereogenic centers). For chiral molecules with several stereogenic centers, does the potentially large number of candidate molecules make nonobvious the one that is pharmacologically most beneficial because there are more possibilities from which to choose?

C. Early Case Law

1. Enantiomers: Lack of Novelty?

¶12 The first time a United States court addressed the patentability of a single enantiomer seems to be in the 1948 case *In re Williams*.³⁸ In *Williams*, the Board of Appeals rejected a claim to a single-enantiomer compound on the grounds of both lack of novelty and lack of invention.³⁹ The lack of novelty rejection was based on a prior art reference that disclosed the production of a compound having a formula identical to the claimed compound. Although the prior art compound was racemic, the reference did not so indicate. The Board of Appeals reasoned that because the enantiomer necessarily existed as part of the disclosed racemate, it could not be novel. 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, although it may, of course, render the claim unpatentable for lack of invention.”⁴⁰ This rule that lack of novelty will not render an enantiomer unpatentable over its previously disclosed racemate has been consistently applied.⁴¹

³⁷ 35 U.S.C. § 101 (2006).

³⁸ 171 F.2d 319 (C.C.P.A. 1948).

³⁹ Lack of invention is now called § 103 obviousness.

⁴⁰ *In re Williams*, 171 F.2d 319, 320 (C.C.P.A. 1948). The Court of Customs and Patent Appeals was the predecessor to the Court of Appeals for the Federal Circuit.

⁴¹ See, e.g., *Pfizer Inc. v. Ranbaxy Labs.*, 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 . . .”). The general rule of the Patent and Trademark Office is that, although “[a] genus does not always anticipate a claim to a species within the genus, . . . when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named.”; *In re May*, 574 F.2d 1082, 1090 (C.C.P.A. 1978) (“The novelty of an optical isomer is not negated by the prior art disclosure of its racemate.”); *Brenner v. Ladd*, 247 F. Supp. 51, 56 (D.D.C. 1965) (“[I]t should be noted that plaintiff’s [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.”). MANUAL OF PATENT EXAMINING PROCEDURE § 2131.02 (8th ed. 2003) [hereinafter MPEP]. However, this is not inconsistent with cited decisions because, for

¶13 To pharmaceutical companies, the novelty of enantiomers over their racemates is a favorable rule. As mentioned previously, many chiral drugs have historically been approved not as single enantiomers, but as racemates. Companies may be able to extend product life or even leverage a competitor's racemic product by making a chiral switch—an industry term for the development of a single-enantiomer drug when the drug in racemic form is already on the market.⁴² For example, Sepracor, a Massachusetts company that markets the single-enantiomer drug Lunesta®, has obtained patents on single-enantiomer versions of sixteen chiral drugs previously sold as racemates by other firms.⁴³

2. Enantiomers: Unpatentable as Obvious?

¶14 Although the novelty and usefulness requirements may easily be met by single enantiomers, the third and greatest hurdle remains: obviousness.⁴⁴ As the *Williams* court suggested in 1948, obviousness may render an enantiomer unpatentable over its previously disclosed racemate even where novelty will not. In *Williams*, a prior art reference disclosed the chemical formula of the racemate, and it was further asserted that the resolution of such a racemate was known to those skilled in the art. However, in holding the single enantiomer nonobvious and therefore upholding the patent, the court emphasized that no evidence was presented to establish that the compound was known to be racemic prior to the date of invention. Therefore, it was not shown that one skilled in the art would have any motivation to resolve it into its component enantiomers.⁴⁵

¶15 From *Williams* it would appear that if a prior art reference discloses the chemical formula of the racemate, but does not disclose that it is racemic, the enantiomer will satisfy the nonobviousness requirement. This rule was limited, however, in the 1960 case of *In re Adamson*.⁴⁶ Like *Williams*, *Adamson* involved prior art references which disclosed the chemical formula of the claimed compound, but did not indicate its racemic nature. Another prior art reference, an organic chemistry text book by Karrer, did not specifically mention the claimed compounds, but did state that that synthetically produced organic compounds containing an asymmetric carbon atom are racemic. It also described several resolution methods, including the one used to resolve the claimed compound. The court held both the product and process claims invalid: “In view of the teachings of Karrer we feel that one of ordinary skill in the stereoisomer and pharmaceutical arts would recognize that the Adamson compounds exist as racemates, hence the fact that no reference to stereoisomerism is made by the Adamson references themselves is of no moment.”⁴⁷ The court specifically distinguished *Williams* on the basis that neither Karrer nor an equivalent reference was cited in that case.

¶16 The Karrer text referred to in *Adamson* is frequently cited in the earlier cases addressing patentability of enantiomers, perhaps because it was one of the few works on stereoisomers available at that time. The stereoisomer arts have not remained static since their inception,⁴⁸ and *Adamson* could be read to suggest that as the state of the art advances it may be increasingly difficult to obtain a patent on a single-enantiomer molecule. As knowledge of enantiomers increases and resolution techniques improve, less inventive genius would be required to make a single enantiomer from its racemate. Indeed, such have been the advances in resolution techniques that last year in a patent

example, there may be no known process for resolving the racemate. MPEP § 2121.02 (8th ed. 2003) (“Where a process for making the compound is not developed until after the date of invention, the mere naming of a compound in a reference, without more, cannot constitute a description of the compound.”).

⁴² Hutt & Valentová, *supra* note 20, at 15. Chiral switches are sometimes referred to as racemic switches.

⁴³ Stephen C. Stinson, *Counting on Chiral Drugs*, CHEM. & ENG'G NEWS, Sept. 21, 1998, at 83, 84.

⁴⁴ Song Huang, *The Nonobviousness Requirements for Biotechnological Inventions: Resolving Uncertainty in Favor of Innovation*, 21 SANTA CLARA COMPUTER & HIGH TECH. L.J. 597 (2005) (noting that obviousness is sometimes referred to as “the ultimate condition of patentability”).

⁴⁵ *In re Williams*, 171 F.2d 319, 320 (C.C.P.A. 1948) (“[T]he idea of resolving it . . . would not occur to one skilled in the art.”).

⁴⁶ *In re Adamson*, 275 F.2d 952 (C.C.P.A. 1960).

⁴⁷ *Id.* at 954.

⁴⁸ Caldwell, *supra* note 8, S70 (noting “recent technological advances that have facilitated the separation . . . of enantiomers”).

dispute over blockbuster drug Lipitor®, the defendant “acknowledge[d] that one skilled in the art would know how to resolve racemates into their constituent enantiomers.”⁴⁹

I. MODERN DAY OBVIOUSNESS

A. *Prima Facie Obviousness*

¶17 It is not only that the stereoisomer arts have advanced significantly since *Adamson* was decided; so too have there been changes and refinements in the law of obviousness. The 1952 Patent Act introduced § 103, stating that “[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.”⁵⁰ From this seemingly simple concept—that one may not obtain a patent on something that is “obvious” in light of what already exists in the prior art—has evolved a rich and sometimes complex body of literature with respect to the chemical and pharmaceutical arts.

1. *Graham v. John Deere Co.*

¶18 It was not until 1966 that *Graham v. John Deere Co.* laid out the basic factors that set forth the current standard for making obviousness determinations.⁵¹ The *Graham* Court noted that § 103 was a codification of the common law concept of “lack of invention” that dated back more than 100 years. The Court then explained: “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.”⁵² Secondary considerations, sometimes called indicia of nonobviousness, are also relevant to the obviousness determination and include commercial success, long felt but unsolved need, and the failure of others.⁵³

¶19 The *Graham* factors apply to obviousness determinations regardless of the art in question. While application of the *Graham* factors is well settled as the standard for making obviousness determinations, applying them to the chemical arts has in practice led to a large number of sometimes conflicting court opinions and generated confusion as to the proper determination of obviousness.⁵⁴

2. *Motivation or Suggestion to Combine*

¶20 With respect to the first *Graham* factor (the scope and content of the prior art), “the relevant inquiry . . . is whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references.”⁵⁵ Generally, this means

⁴⁹ Pfizer Inc. v. Ranbaxy Labs., 405 F. Supp. 2d 495, 505 (D. Del. 2005).

⁵⁰ 35 U.S.C. § 103(a) (2006).

⁵¹ 383 U.S. 1, 17-18 (1966).

⁵² *Id.*

⁵³ *Id.* Secondary considerations *must* be considered before making an obviousness determination. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986).

⁵⁴ *In re* Dillon, 919 F.2d 688, 700 (Fed. Cir. 1990) (Newman, J., dissenting) (“[t]he holdings of the prior law [regarding prima facie obviousness] were not entirely consistent”); *In re* Stemninsky, 444 F.2d 581, 585 (C.C.P.A. 1971) (acknowledging “this court’s failure to render consistent precedent over the years”); Philippe Ducor, *Recombinant Products and Nonobviousness: A Typology*, 13 SANTA CLARA COMPUTER & HIGH TECH. L.J. 1, 17 (1997) (“The case law is very technical and sometimes conflicting”); William D. Marsillo, *How Chemical Nomenclature Confused the Courts*, 6 U. BALT. INTELL. PROP. L.J. 29, 31 (1997) (describing obviousness based on structural similarity as a “troublesome area of patent law.”); *id.* at 34 (“Prima facie obviousness based on structural similarity between a claimed species and a prior art genus that includes the claimed species has proven to be a particularly difficult area for the courts to maintain a consistent jurisprudence.”).

⁵⁵ Ruiz v. A.B. Chance Co., 234 F.3d 654, 664 (Fed. Cir. 2000); *In re* Mayne, 104 F.3d 1339, 1342 (Fed. Cir. 1997) (“When relying on numerous references or a modification of prior art, it is incumbent upon the examiner to identify some suggestion to combine references or make the modification.”); *In re* Ochiai, 71 F.3d 1565, 1570 (Fed. Cir. 1995) (“The mere chemical possibility that one of those prior art acids could be modified such that its use would lead to the particular cephem recited in claim 6 does not make the process recited in claim 6 obvious ‘unless the prior art suggested the desirability of [such a] modification.’”); *In re* Jones, 958 F.2d 347, 351 (Fed. Cir. 1992) (stating that there must be some suggestion to combine, “either in the references themselves or in the knowledge generally available to one of ordinary skill in the art”).

that to establish a prima facie case of obviousness, one must show “some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art that would lead that individual to combine the relevant teachings of the references.”⁵⁶

¶21 In the case of enantiomers, the references in question might include one that discloses a racemic compound and one or more others that describe resolution processes. As stated previously, it is well known in the art that enantiomers frequently exhibit different levels of activity from one another and that each enantiomer may not be equally responsible for side effects. Achieving higher pharmacological activity level at lower dosage levels and with fewer side effects will generally be desirable,⁵⁷ and it has been suggested in the literature that companies should attempt to separate enantiomers, assess the contribution of individual stereoisomers to the activity of interest, and select which stereoisomer to market.⁵⁸ Therefore, one skilled in the pharmaceutical arts would, at least in some cases, be motivated to combine a reference teaching a racemate with references indicating that single enantiomers may exhibit more desirable properties to attempt to isolate one or both enantiomers.

¶22 There is a second line of reasoning suggesting that sufficient motivation exists to resolve pharmaceutically-relevant racemates. In view of the extensive literature on the topic and single-enantiomer drugs already on the market or in development, one ordinarily skilled in the stereoisomer and pharmaceutical arts would be aware of the potential benefits of single-enantiomer molecules. The Federal Circuit has indicated that knowledge of persons ordinarily skilled in the art can serve as a source of motivation to combine references.⁵⁹ Furthermore, obviousness may be based on a single prior art reference where there is a suggestion to modify the teachings of that reference.⁶⁰ Therefore, motivation to isolate an enantiomer could potentially be found in a single reference disclosing the racemate.

¶23 Along these lines, one court found the prior art to provide “ample motivation to separate the optical isomers [of the racemate].”⁶¹ The court stated that given “the development of synthesis methods via stereoselection and improvement in the analytical methods of optical isomers in the recent years, many came to believe that only one of the enantiomers is the important substance and that the other is . . . almost an impure substance.”⁶² Another court found that that the prior stereoisomer art as late as 1991 did not yet provide the requisite motivation to resolve racemates into their constituent enantiomers.⁶³ The court reasoned that resolution into component enantiomers could at best be expected to yield a two-fold increase in activity,⁶⁴ the benefit of which would be offset by the difficulty and complexity of the resolution process, as well as other drawbacks.⁶⁵

¶24 While there may be some degree of tension between these two cases, it is important to remember that obviousness is a fact-specific inquiry. Care must be taken not to apply a general principle indiscriminately to specific circumstances. Simply because a racemate has been disclosed

⁵⁶ *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984).

⁵⁷ *Mansfield et al.*, *supra* note 29, at 287 (“[I]he most important motivation for developing enantiomers has been a genuine desire to improve efficacy and reduce adverse effects of drugs . . .”).

⁵⁸ *Caldwell*, *supra* note 8, at S69; *Israel Agranat et al.*, *Putting Chirality to Work: The Strategy of Chiral Switches*, NATURE REVIEWS DRUG DISCOVERY, Oct. 2002, at 753, 755.

⁵⁹ *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

⁶⁰ *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000); JEROME ROSENSTOCK, THE LAW OF CHEMICAL AND PHARMACEUTICAL INVENTION, PATENT AND NONPATENT PROTECTION § 8.01[F] (2d ed. 1998) (“It is to be noted that a finding of obviousness in view of a single prior art reference is not unusual.”).

⁶¹ *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 752 (N.D. W. Va. 2004).

⁶² *Id.*

⁶³ *Pfizer Inc. v. Ranbaxy Labs.*, 405 F. Supp. 2d 495, 517 (D. Del. 2005).

⁶⁴ Presumably, the two-fold limit is imposed by the fact that even if 100% of the activity level results from only one enantiomer, and the other is completely inactive, removing the inactive enantiomer will simply double the activity level per unit of compound. If both enantiomers are somewhat active, removing the less active one would increase the activity level by something less than 100%.

⁶⁵ *Ranbaxy*, 405 F. Supp. 2d at 517. See also *Ortho-McNeil*, 348 F. Supp. 2d at 747 (also noting that a two-fold difference in activity is the maximum possible difference in activity level between a racemate and its enantiomer).

does not necessarily mean that motivation exists to resolve it. For example, a reference disclosing a racemate might suggest that each enantiomer is equally responsible for side effects (or beneficial effects), that the enantiomers interconvert *in vivo*,⁶⁶ that the compound is pharmaceutically unsuitable (for example, due to toxicity or bioinstability), etc.

¶25 This type of disclosure in the prior art which actively discourages the claimed invention is said to “teach away” from the invention, and would make a finding of obviousness less likely.⁶⁷ Teaching away could also arise in the context of chiral molecules by a suggestion that a particular method of resolution should not work with a particular type of chiral molecule. If an inventor nevertheless combines that resolution method with the particular chiral molecule to resolve the racemate, the resulting enantiomer would more likely be held nonobvious.

3. *Size of the Genus*

¶26 Generally speaking, the larger the genus, the less likely that a species within that genus will be held obvious, and vice versa.⁶⁸ A “broad” genus, therefore, does not necessarily render obvious each compound within its scope.⁶⁹ It is not clear how many species a genus must contain before it can be considered “broad.” Species have been held obvious over the disclosure of a genus containing 1200 compounds, where the prior art also disclosed that any member of the genus would have “desirable sodium and potassium eliminating properties.”⁷⁰ At the other extreme, a genus containing 10³⁶ members did not render a species claim obvious.⁷¹ Unfortunately, the case law does not provide enough data points to determine at what point, if any, the size of the genus would be unlikely to render the species obvious.⁷²

¶27 In some cases, a small genus can even anticipate (and not merely render obvious) a species, even if the species is not specifically named.⁷³ In *In re Petering*, a prior art reference disclosing a limited genus of twenty compounds rendered every species within the genus unpatentable.⁷⁴ The court emphasized, however, that it “is not the mere number of compounds . . . which is significant . . . but, rather, the total circumstances involved”⁷⁵

¶28 In the case of enantiomers with one chiral center, the genus contains exactly two species, which is a very small genus.⁷⁶ Although size alone cannot support an obviousness rejection,⁷⁷ this factor weighs strongly in favor of obviousness.

⁶⁶ Olivier Blin, *Separation des Enantiomers: Pour Quelle Amelioration du Rapport Benefice/Risque?*, THERAPIE, Nov.-Dec. 2004, at 625, 626.

⁶⁷ *Alza Corp. v. Mylan Labs. Inc.*, 388 F. Supp. 2d 717, 738 (N.D. W. Va. 2005) (“A finding that a prior art reference ‘teaches away’ from combining references can alone defeat an obviousness claim.”).

⁶⁸ ROSENSTOCK, *supra* note 60, at § 8.02[D] (“[W]here a genus or generic formula has a relatively small number of variables, that is, substituents, then a prima facie case of obviousness can be made out. One the other hand, where the genus or generic formula disclosed in the prior art has a relatively large number of substituents that can be made, a showing of obviousness is not so readily accomplished.”).

⁶⁹ *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992) (“We decline to extract from *Merck* the rule that the Solicitor appears to suggest – that regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it Every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts.”).

⁷⁰ *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989).

⁷¹ *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993); *see also In re Baird*, 16 F.3d at 383 (holding nonobvious three claimed species over a prior art genus of more than 100 million species).

⁷² *See* Jeffery Fredman, *Are Oligonucleotide Primers and Probes Prima Facie Obvious Over Larger Prior Art Nucleic Acids?*, 19 SANTA CLARA COMPUTER & HIGH TECH. L.J. 285, 301 (2002) (discussing *In re Baird* and *In re Bell* and noting that the Federal Circuit, “when given cases where the genus was substantially larger [than the 1200-member genus of *Merck*], has stepped away from the bright line rule . . . that species are prima facie obvious where the genus was in the prior art.”).

⁷³ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) (citing *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1380 (Fed. Cir. 2001)).

⁷⁴ *In re Petering*, 301 F.2d 676 (C.C.P.A. 1962).

⁷⁵ *Id.* at 681.

⁷⁶ Of course, as the number of chiral centers increases, so too does the size of the genus.

⁷⁷ Guidelines for the Examination of Claims Directed to Species of Chemical Compositions Based Upon a Single Prior Art Reference, 63 Fed. Reg. 47,000, 47,002 (Sept. 3, 1998).

4. Structural Similarity

¶29

In the chemical arts the *Graham* factors have been interpreted such that “a prima facie case of obviousness requires ‘structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.’”⁷⁸ Although both courts and commentators have indicated that structural similarity by itself has sometimes been held to provide the requisite motivation,⁷⁹ an examination of the cases cited reveals that the prior art in those cases disclosed something more than mere structural similarity. For example, in *In re May*, the prior art not only disclosed the racemate of the claimed enantiomer, but also suggested that the claimed enantiomer would possess one of the desired pharmaceutical properties.⁸⁰ In any event, the appellants in *May* conceded prima facie obviousness, so the court was not able to render a holding regarding the issue of prima facie obvious based on structure alone.⁸¹ Similarly, in *In re Wilder*, the prior art disclosed not only a homologue of the claimed compound but also a similar process of manufacture and similar uses as those of the claimed compound.⁸² Furthermore, the court did not separately address the issue of prima facie obviousness, focusing instead on whether or not Wilder had successfully overcome the prima facie showing.⁸³ Finally, in *In re Merck & Co.*, the prior art not only disclosed a similar compound but “expressly stated that [the claimed compound] was expected to resemble [the prior art compound] clinically in its depression alleviation effects.”⁸⁴

¶30

Nevertheless, in the case of enantiomers that are used as pharmaceuticals, structure “alone” is probably sufficient to create a prima facie case of obviousness in many cases. The Federal Circuit seems to accept this proposition.⁸⁵ More specifically, the prior art would satisfy the Federal Circuit’s standard of prima facie obviousness that requires “structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.”⁸⁶ With a claimed enantiomer, the structurally similar prior art in question will frequently consist of a racemate that is already used as a pharmaceutical. There is always a motivation in the pharmaceutical industry to obtain products with improved properties.⁸⁷ Thus, as prior art, the pharmaceutically active racemate would provide both a nearly identical structure and the motivation to obtain the enantiomer.⁸⁸

⁷⁸ *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)). *see In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“When a chemical composition is claimed, a prima facie case of obviousness under § 103 may be established by the PTO’s citation of a reference to a similar composition, the presumption being that similar compositions have similar properties.”).

⁷⁹ *See, e.g., In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (“Structural relationships often provide the requisite motivation”); *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985) (“When chemical compounds have ‘very close’ structural similarities and similar utilities, without more a prima facie case may be made.”) (citing *In re Wilder*, 563 F.2d 457 (C.C.P.A. 1977) (adjacent homologs and structural isomers); *In re May*, 574 F.2d 1082, 1086 (C.C.P.A. 1978); and *In re Hoch*, 428 F.2d 1341 (C.C.P.A. 1970) (acid and ethyl ester)); ROSENSTOCK, *supra* note 60, at § 8.02[A][1] (stating that “[t]he courts and the USPTO have indicated that a homologous series raises a prima facie case of obviousness,” but citing older cases whose continued validity is questionable); Lissy, *supra* note 3, at 1080-81 (“Several cases have suggested that structural similarity alone may give rise to a prima facie case . . . [which result is only] consistent with *Dillon* if the state of knowledge in the field does in fact provide the motivation of likelihood of success.”) (citing *In re Merck & Co.*, 800 F.2d 1091, 1096 (Fed. Cir. 1986) and *In re Payne*, 606 F.2d 303, 313 (C.C.P.A. 1979) (pesticides which were neither true isomers nor homologues)); *see also In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) (“[A] known compound may suggest its analogs or isomers, either geometric isomers . . . or position isomers . . .”).

⁸⁰ *In re May*, 574 F.2d at 1086.

⁸¹ *Id.* at 1089.

⁸² *In re Wilder*, 563 F.2d at 459.

⁸³ *Id.* at 460.

⁸⁴ *In re Merck & Co.*, 800 F.2d at 1096.

⁸⁵ *See, e.g., In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (“Structural relationships often provide the requisite motivation. . . .”); *In re Dillon*, 919 F.2d 688, 697 (Fed. Cir. 1990) (“The reference disclosed a lower homolog of the claimed compounds, so it was clear that impliedly a prima facie case existed.”).

⁸⁶ *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (quoting *In re Dillon*, 919 F.2d at 692).

⁸⁷ *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) (“[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.”). *See also Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 777 F. Supp. 330, 353-54 (D. Del. 1991); *Yamanouchi*, 231 F.3d at 1341.

⁸⁸ *But see* MPEP § 2144.09 (8th ed. 2003) (“Isomers having the same empirical formula but different structures are not

¶31 On the other hand, the Federal Circuit has stated that when a prima facie case of obviousness based on structural similarity is made, the presumption is that “similar compositions have similar properties.”⁸⁹ As noted previously, similar properties cannot necessarily be presumed with respect to chiral molecules, since each enantiomer can exhibit significantly different *in vivo* behavior. However, the requirement is one of “similar” properties, not “identical” properties. Where a single enantiomer is used to treat the same condition as the racemate, this may be sufficient to constitute similar properties even if the efficacy is greater and side effects are fewer.

¶32 Regardless of how this issue is resolved, whether and when similar structure suggests similar properties is a two-edged sword for those attempting to demonstrate obviousness. On the one hand, asserting that similar structures can normally be expected to have similar properties might help to show that one skilled in the art would be motivated to make the new compound, and thus weigh in favor of obviousness. On the other hand, the same assertion could establish a baseline of expected properties against which to measure actual properties. If it can be shown that the newly discovered compound exhibits properties that are a substantial improvement over the prior art compound, this would tend to establish unexpected results and thereby rebut an obviousness showing.

5. Reasonable Expectation of Success

¶33 Motivation to combine references will be found only where there is a “reasonable expectation of success.”⁹⁰ While the researcher cannot be certain that one enantiomer will be superior as to all relevant properties, absolute predictability is not required in order to reach the conclusion that an invention is obvious.⁹¹ Furthermore, with respect to racemates there must be a reasonable expectation not only that the single enantiomer will exhibit desirable properties, but also that it will be possible to resolve the racemate in the first place.⁹²

¶34 In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories Inc.*, the court held that under the “reasonable expectation of success” standard, the defendant had to prove that the prior art would not only motivate a person of ordinary skill in the art to make the enantiomer, but also reasonably suggest that the enantiomer would exhibit its “unique combination of properties.”⁹³ The combination of properties of the enantiomer in question included double the potency, ten times greater solubility, and appreciably lower toxicity than the prior art.⁹⁴ Requiring this particular unique combination of properties is a relatively stringent standard, however, and should not be interpreted too strictly.⁹⁵ It would be nearly impossible for the prior art to suggest the “unique combination of

necessarily considered equivalent by chemists skilled in the art and therefore are not *necessarily* suggestive of each other.” (emphasis added)).

⁸⁹ *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“When a chemical composition is claimed, a prima facie case of obviousness under § 103 may be established by the PTO’s citation of a reference to a similar composition, the presumption being that similar compositions have similar properties.”); *In re Geiger*, 815 F.2d 686, 688 (Fed. Cir. 1987) (“An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.”); *In re Gyurik*, 596 F.2d 1012, 1018 (C.C.P.A. 1979) (“In obviousness rejections based on close similarity in chemical structure, the necessary motivation to make a claimed compound . . . rises from the expectation that compounds similar in structure will have similar properties.”); *In re May*, 574 F.2d 1082, 1094 (C.C.P.A. 1978) (“[T]he basis of the prima facie case of obviousness, at least to a major extent, is based on the presumed expectation that compounds which are similar in structure will have similar properties.”).

⁹⁰ *Alza Corp. v. Mylan Labs. Inc.*, 388 F. Supp. 2d 717, 737 (N.D. W. Va. 2005) (“The inspiration to combine prior art references must also offer a ‘reasonable expectation of success.’” (quoting *In re O’Farrell*, 853 F.2d 894, 904 (Fed. Cir. 1988))); *see also Pfizer Inc. v. Ranbaxy Labs.*, 405 F. Supp. 2d 495, 517 (D. Del. 2005) (finding that it may have been obvious “to try various salts in an attempt to find a salt with properties suitable for pharmaceutical use,” but that there would not have been a reasonable expectation to succeed with calcium, a particular salt).

⁹¹ *See, e.g., In re Longi*, 759 F.2d 887, 896 (Fed. Cir. 1985) (“Only a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness.”); *In re Payne*, 606 F.2d 303, 313 (C.C.P.A. 1979).

⁹² *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 752-53 (N.D. W. Va. 2004) (concluding that, as of 1984, the resolution of the particular enantiomers in question would have been a “logical extension of the prior art” though not “a routine matter”).

⁹³ *Id.* at 749.

⁹⁴ *Id.* at 754.

⁹⁵ *See, e.g., In re Payne*, 606 F.2d at 316 (“A finding of obviousness is not precluded . . . when only some, but not all, of the properties of a claimed compound are predictable from the prior art.”).

properties” of a molecule that has not yet been isolated. It should be enough that the prior art provides a reasonable expectation that the enantiomer will possess at least one significantly improved property, as well as exhibit a combination of properties that would make the compound pharmaceutically acceptable.⁹⁶ Given the number of potential properties and the infinite possible magnitudes of each, anything more would impose a requirement of clairvoyance, not reasonable expectation.

¶35 To support its interpretation of “reasonable expectation of success,” the *Ortho-McNeil* court cites *Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.*, in which it was stated that “success was finding a compound that had high activity, few side effects, and lacked toxicity.”⁹⁷ However, this statement must be viewed in context. In *Yamanouchi*, the party attempting to show “reasonable expectation of success” had merely demonstrated that an ordinary medicinal chemist would reasonably have expected the claimed compound to exhibit a baseline level of pharmacological activity. The *Yamanouchi* court noted that there were “tens of thousands” of compounds that exhibited this baseline level of activity, and that the claimed compound exhibited a level of activity 165 times greater than this in addition to having a desirable combination of pharmaceutical properties.⁹⁸

¶36 Recall that reasonable expectation of success is a concept relevant to a showing of motivation to combine prior art references.⁹⁹ That is, without a reasonable expectation of success, one reasonably skilled in the art would have no motivation to combine references. Requiring a reasonable expectation of significant improvement in at least one property as well as an acceptable combination of other properties (not necessarily the particular combination of the claimed compound) would provide this motivation. Rather than requiring an expectation of the precise combination of properties possessed by the claimed invention, the *Yamanouchi* court was merely emphasizing that something more than an expectation of baseline activity was required in light of the fact that thousands of compounds would exhibit this property. Indeed, the case cited by *Yamanouchi* regarding reasonable expectation of success affirms that “[o]nly a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness.”¹⁰⁰

¶37 At the same time, one must be cautious to not set the bar for reasonable expectation of success too low. “‘Obvious to try’ has long been held not to constitute obviousness.”¹⁰¹ Thus one might argue that, absent any particular motivation provided by the prior art, isolating a single enantiomer would merely be “obvious to try” but would not necessarily render the single enantiomer obvious. As the Federal Circuit has noted, however, “the admonition that ‘obvious to try’ is not the standard under § 103 has been directed mainly at two kinds of error,”¹⁰² neither of which applies to enantiomers. The first is where “what would have been ‘obvious to try’ would 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.”¹⁰³ With a given racemate and its two enantiomers, there are at most two possible choices, not “numerous” or “many” possible choices.

¶38 The second main category of error where an invention that is obvious to try might nevertheless be held nonobvious is where the prior art suggests exploring a new technology or general approach but gives “only general guidance as to the particular form of the claimed invention or how to achieve

⁹⁶ *In re Dillon*, 919 F.2d 688, 693 (Fed. Cir. 1990) (“[T]he statement that a prima facie obviousness rejection is not supported if no reference shows or suggests the newly-discovered properties and results of a claimed structure is not the law.”).

⁹⁷ 231 F.3d 1339, 1345 (Fed. Cir. 2000).

⁹⁸ *Id.*

⁹⁹ *Alza Corp. v. Mylan Labs. Inc.*, 388 F. Supp. 2d 717, 737 (N.D.W. Va. 2005).

¹⁰⁰ *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985).

¹⁰¹ *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

¹⁰² *Id.*

¹⁰³ *Id.*

it.”¹⁰⁴ In the case of enantiomers, one of two precise compounds is suggested by a given prior art racemate. Those skilled in the art need not consider which combinations of substituents are likely to produce compounds with desirable properties. While the process necessary to resolve a given racemate may not be obvious, it can hardly be said that the mere selection of an enantiomer in light of its known racemate constitutes innovation exceeding the abilities of one ordinarily skilled in the art. Indeed, it is not inconceivable that an employee in the marketing department of a pharmaceutical company might suggest a chiral switch.

6. Conclusion as to Prima Facie Obviousness

¶39 It is tempting to conclude based on the above discussion that enantiomers will generally be held prima facie obvious over their previously disclosed racemates or their enantiomers of opposite rotation. The chemical structure of each enantiomer is nearly identical, a disclosed racemate is a genus that contains only two species, there is ample suggestion in the pharmaceutical arts to generally motivate the resolution of pharmaceutically relevant racemates, and in light of recent advances in resolution techniques there is an increased likelihood of success in obtaining a selected enantiomer.

¶40 In fact, a number of courts have ruled consistently with this line of reasoning. In 1997, the U.S. District Court for the Northern District of Georgia stated in dicta that “disclosure of the racemate or racemic mixture makes prima facie obvious the separate enantiomers of that racemate.”¹⁰⁵ Nor was the Georgia court breaking new ground in its determination. More than thirty years earlier, the District Court for the District of Columbia arrived at this same conclusion: “[I]n the absence of unexpected or unobvious beneficial properties, an optically active isomer [i.e., an enantiomer] is unpatentable over either the isomer of opposite rotation or, as in this case, the racemic compound itself.”¹⁰⁶ As of 1969, this principle was apparently so well established that one appellant did not even contest prima facie obviousness, conceding that “under existing law a [stereoisomer] is not patentable over its known racemic mixture unless it possesses unexpected properties not possessed by the racemic mixture.”¹⁰⁷ In 1992, the Federal Circuit acknowledged these and other cases by stating in dicta that “[p]articular types or categories of structural similarity without more have, in past cases, given rise to prima facie obviousness,”¹⁰⁸ and reaffirmed this position in 1995 when it stated that, “[w]hen a chemical composition is claimed, a prima facie case of obviousness under §103 may be established by the PTO’s citation of a reference to a similar composition, the presumption being that similar compositions have similar properties.”¹⁰⁹

¶41 However, it would be a mistake to conclude that under the current state of the law an enantiomer will in all cases be prima facie obvious over either its mirror image enantiomer or its racemate. Indeed, the Federal Circuit has stated that “generalization is to be avoided insofar as specific structures are alleged to be prima facie obvious one from the other.”¹¹⁰ Citing this and other statements of the Federal Circuit, the District Court for the Northern District of West Virginia recently refused to accept the assertion that an enantiomer was prima facie obvious vis-à-vis its racemate.¹¹¹ And in a 2002 non-precedential decision, the Board of Patent Appeals and Interferences

¹⁰⁴ *Id.*

¹⁰⁵ *Emory Univ. v. Glaxo Wellcome Inc.*, 44 U.S.P.Q.2d 1407, 1414 (N.D. Ga. 1997) (but also noting that “if 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”).

¹⁰⁶ *Brenner v. Ladd*, 247 F. Supp. 51, 56 (D.D.C. 1965); *see also Sterling Drug, Inc. v. Watson*, 135 F.Supp. 173 (D.D.C. 1955) (holding an otherwise obvious enantiomer nevertheless patentable over its racemate based on unexpected results, failure of others, and commercial success).

¹⁰⁷ *In re Anthony*, 414 F. 2d 1383 (C.C.P.A. 1969).

¹⁰⁸ *In re Jones*, 958 F.2d 347, 349-50 (Fed. Cir. 1992). *See also In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985) (“When chemical compounds have ‘very close’ structural similarities and similar utilities, without more a prima facie case may be made.”).

¹⁰⁹ *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). *In re Dillon*, 919 F.2d 688, 698 (Fed. Cir. 1990) (similar properties may normally be presumed when compounds are very close in structure).

¹¹⁰ *In re Jones*, 958 F.2d at 350 (citing *In re Grabiak*, 769 F.2d at 731); *see also In re Lancer*, 465 F.2d 896, 899 (C.C.P.A. 1972) (“Homology should not be automatically equated with prima facie obviousness . . .”).

¹¹¹ *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 749 n.19 (N.D. W. Va. 2004).

noted that the disclosure of one enantiomer does not necessarily create a prima facie case of obviousness as to the other enantiomer.¹¹²

¶42 Whether or not an enantiomer is prima facie obvious in light of its racemate may well turn on the definitions of “reasonable expectation” and “success,” neither of which has yet been defined with precision. Success should require at a minimum that the single enantiomer be superior to the racemate in some way. If it were not superior in any way, what motivation would the intensely practical researcher have to resolve the racemate?¹¹³ The courts have unequivocally stated that reasonable expectation requires something less than absolute predictability, but how much less is not clear. Should reasonable expectation require a greater than 50% probability of success (similar to the preponderance of the evidence standard)? Or simply that the probability of success be more than negligible (the inverse of the beyond reasonable doubt standard)?

B. Overcoming Obviousness

1. Obviousness and Prima Facie Obviousness Distinguished

¶43 Prima facie obviousness must not, of course, be confused with the ultimate determination of obviousness. In holding that no prima facie case of obviousness had been established, the *Ortho-McNeil* court noted that *Graham* findings must be made to establish a prima facie case of obviousness.¹¹⁴ The first case cited by the *Ortho-McNeil* court, *In re Mayne*, states that *Graham* factors are the foundational facts in the prima facie determination, that secondary considerations “are relevant to the determination of obviousness,” and that “each obviousness determination rests on its own facts.”¹¹⁵ It is important to note that these latter two quotations refer to *obviousness*, not prima facie obviousness. Similarly, the portion of *A.B. Chance* cited by *Ortho-McNeil* refers to obviousness, not prima facie obviousness.¹¹⁶ *A.B. Chance* later notes that secondary considerations may be sufficient to *overcome* a prima facie case of obviousness.¹¹⁷ Thus, while courts sometimes refer to “the four *Graham* factors,”¹¹⁸ it is only the first three *Graham* factors that are considered when making a prima facie obviousness determination.^{119, 120}

¶44 Prima facie obviousness is a procedural tool, used to shift the burden of proof to the applicant.¹²¹ 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.

¶45 There is no question that the ultimate determination of obviousness must rest on more than structure alone. It is frequently noted that “[f]rom the standpoint of patent law, a compound and all of its properties are inseparable”¹²² Thus in the determination of obviousness courts must

¹¹² *Ex parte Bonfils*, 64 U.S.P.Q.2d (BNA) 1456, at *15-16 (B.P.A.I. 2002).

¹¹³ See *In re Stemniski*, 444 F.2d 581, 586 (C.C.P.A. 1971). Note that this in effect imposes a higher standard than does the § 101 utility requirement, under which an invention may be patentable even if it is no better than, or in fact not as good as, existing products.

¹¹⁴ *Ortho-McNeil*, 348 F. Supp. 2d at 749 n.19.

¹¹⁵ *In re Mayne*, 104 F.3d 1339, 1341 (Fed. Cir. 1997).

¹¹⁶ *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 663 (Fed. Cir. 2000).

¹¹⁷ *Id.* at 667.

¹¹⁸ See, e.g., *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1480 (Fed. Cir. 1997); *Emergency Fuel, LLC v. Pennzoil-Quaker State Co.*, 293 F. Supp. 2d 569, 585 n.23 (D. Md. 2003).

¹¹⁹ Guidelines for the Examination of Claims Directed to Species of Chemical Compositions Based Upon a Single Prior Art Reference, 63 Fed. Reg. 47,000, 47,002 (Sept. 3, 1998) (noting that, in establishing a prima facie obviousness case, office personnel should make findings as to the first three *Graham* factors).

¹²⁰ It should be noted that the *Ortho-McNeil* court does in fact base its conclusion of prima facie obviousness on the first three *Graham* factors.

¹²¹ *In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984) (“The concept of *prima facie* obviousness . . . is but a procedural mechanism”); *Ducor*, *supra* note 54, at 15.

¹²² *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963).

consider not only structure, but also properties.¹²³ However, this statement goes not to the *prima facie* determination of obviousness, but to the ultimate determination.¹²⁴ More generally, the Federal Circuit has stated that “reliance on *per se* rules of obviousness is legally incorrect and must cease.”¹²⁵

2. *Unexpected Results*

¶46 One way to overcome a *prima facie* case of obviousness is to show that the enantiomer “exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected” despite the disclosures of the prior art.¹²⁶ Thus, if an enantiomer exhibits one or more properties which are superior to and unexpected in light of the known properties of the racemate, the enantiomer may be patentable despite a high degree of structural similarity. Looked at another way, unexpected results can show that a claimed compound that appeared to be obvious on structural grounds was not obvious when looked at as a whole.¹²⁷ This is a sensible exception to the obviousness standard, for the simple reason that “that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.”¹²⁸

¶47 Where a given pharmaceutical is already being marketed as a racemic mixture, the most likely difference between the racemate and the enantiomer may be the level of pharmacological activity. An increased efficacy level can, at least in some cases, constitute an “unexpected result.”¹²⁹ However, “since structurally similar compounds generally have similar properties, an unexpected result must be a substantial improvement over the prior art.”¹³⁰ Recently, *Ortho-McNeil* held that it would not have been expected that an enantiomer would be “twice as potent, about ten times more soluble, and appreciably less toxic” than its racemate.¹³¹ It emphasized that, even if the prior art suggested improvements in one or two properties of the enantiomer over the racemate, the *combination* of improved properties was unexpected.¹³² However, improvements in multiple properties are not necessary to rebut obviousness; significant improvement in one of a spectrum of common properties can be sufficient.¹³³

¶48 What constitutes “significant improvement” in one property? Is there a minimum multiple of increased potency that is required before “significant improvement” will be found? It appears that the answer is no, and that the relevant inquiry is rather whether the prior art suggested the degree of

¹²³ *Eli Lilly & Co. v. Zenith Goldline Pharma, Inc.*, 2001 WL 1397304, at *6 (S.D. Ind. Oct. 29, 2001) (“Obviousness cannot be determined by chemical structure alone.”).

¹²⁴ *In re Dillon*, 919 F.2d 688, 697 (Fed. Cir. 1990) (“Properties, therefore, *are* relevant to the creation of a *prima facie* case in the sense of affecting the motivation of a researcher to make compounds closely related to or suggested by a prior art compound, but it is not required, as stated in the dissent, that the prior art disclose or suggest the properties newly-discovered by an applicant in order for there to be a *prima facie* case of obviousness. . . . *Papesch*, however, did not deal with the requirements for establishing a *prima facie* case. . . .” (emphasis in original)).

¹²⁵ *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995). The Patent Office has adopted this position. MPEP § 2144.08 (8th ed. 2003) (“Use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103.” (citing *In re Brouwer*, 77 F.3d 422, 425 (Fed. Cir. 1996), *In re Ochiai*, 71 F.3d at 1572, and *In re Baird*, 16 F.3d 380, 382, (Fed. Cir. 1994))).

¹²⁶ *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (noting that “[t]he principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results”); *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 749 (N.D. W. Va. 2004); *In re Dillon*, 919 F.2d at 692 (en banc) (rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties).

¹²⁷ See, e.g., *In re Papesch*, 315 F.2d 381, 391 (1963).

¹²⁸ *In re Soni*, 54 F.3d at 750.

¹²⁹ *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *U.S. v. Ciba-Geigy Corp.*, 508 F. Supp. 1157, 1169 (D. N.J. 1979) (Ten times greater potency resulted in “a significant enough [difference] to be deserving of a patent”); *In re Wiechert*, 370 F.2d 927, 932 (C.C.P.A. 1967) (“In the case at bar, we are impressed by the 7-fold improvements in activity and, in the absence of valid countervailing evidence, we find the claimed compounds to be unobvious.”).

¹³⁰ *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 749 (N.D. W. Va. 2004).

¹³¹ *Id.* at 754-55.

¹³² *Id.* at 754 (the enantiomer “represents the unusual case in which each of its desired properties is superior to . . . those of [the racemate].”).

¹³³ *Ortho-McNeil*, 348 F. Supp. 2d at 754 (even absent the combination of improved properties, a skilled artisan could not even have expected that the enantiomer would be twice as potent as the racemate); *In re Chupp*, 816 F.2d at 646 (evidence that the compound or composition possesses superior and unexpected properties in one of a spectrum of common properties can be sufficient to rebut a *prima facie* case of obviousness).

improvement that is exhibited in the claimed compound.¹³⁴ In *In re Carabateas*, the prior art suggested at most a four to eight-fold increase in activity level, whereas the applicant's compound exhibited a nineteen-fold increase.¹³⁵ In a concurring opinion, Judge Rich suggested that it was the difference between the expected improvement and the observed improvement that should be controlling.¹³⁶ That is, merely because the new compound exhibits a (seemingly large) nineteen-fold increase, this will only be evidence of nonobviousness if the prior art suggested something substantially less than a nineteen-fold increase.

¶49 Exactly how much less is not clear. In *Ortho-McNeil*, the court found that a mere two-fold increase was unexpected, even in light of a prior art showing that some increase might be expected.¹³⁷ In *In re Soni*, the Federal Circuit seemed to adopt the principle that prima facie obviousness can be overcome by demonstrating substantially improved results over what the prior art would have suggested.¹³⁸ However, it then muddled the legal standard by holding that, "when an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary."¹³⁹ As the dissent pointed out, this holding appears to remove the requirement that a showing be made as to the particular level of activity suggested by the prior art, and then compare *that* level of activity to the observed level.¹⁴⁰ In other words, when establishing unexpected results, it should not be enough to merely show that the claimed compound exhibited a substantially higher level of activity than prior art compound. It must be a substantial improvement *over the improvement that was suggested by the prior art*.

¶50 The properties of chemical compounds *in vivo* are generally considered to be unpredictable.¹⁴¹ Specifically with respect to stereoisomers, it is well known that different enantiomers of the same chiral compound can have very different pharmacological properties.¹⁴² It has been suggested that the difficulty in predicting the pharmacological properties of racemates and their enantiomers may result in therapeutically useful compounds being overlooked.¹⁴³ Even if one enantiomer is known to possess a desired property, the other enantiomer could be completely inactive, have some activity, be an antagonist as to its mirror image, or have separate but desirable activity.¹⁴⁴ If it is difficult to

¹³⁴ *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995).

¹³⁵ *In re Carabateas*, 357 F.2d 998, 1001 (C.C.P.A. 1966) (Rich, J., concurring).

¹³⁶ *Id.* at 1001 ("[T]he art makes no suggestion whatever that a reversal of the ester linkage would result in an increased activity approximately the nineteen-fold increase found by appellant. At the very best, the art suggests an increase of the order of four to eight times The question is not, it seems to me, whether the art suggests an improvement, but rather whether it reasonably suggests the particular improvement relied upon for patentability in both its qualitative and quantitative sense.")

¹³⁷ *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 749 (N.D. W. Va. 2004). This finding is perhaps not surprising since a two-fold increase is the maximum increase possible for one enantiomer over its racemate.

¹³⁸ *In re Soni*, 54 F.3d at 750-51.

¹³⁹ *Id.* at 751 (Fed. Cir. 1995) (emphasis added).

¹⁴⁰ *Id.* at 754 (Fed. Cir. 1995) (Michel, C.J., dissenting) ("Neither the specification nor any post-rejection submission contains objective evidence tending to establish either (1) a baseline of expected improvements against which to measure the observed improvements, or (2) the lack of any such baseline expectation in the relevant prior art, as a result of which all degrees of improvement would be unexpected.")

¹⁴¹ *Ducor*, *supra* note 54, at 16; *Glastetter v. Novartis Pharm. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001) ("Even minor deviations in molecular structure can radically change a particular substance's properties and propensities."); 2 DONALD S. CHISUM, *CHISUM ON PATENTS* § 5.04[6] at 5-429 (2000) ("Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known and existing compounds and yet exhibit very different properties."); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 2001 WL 1397304 (S.D. Ind. Oct. 29, 2001) ("The unpredictable nature of chemical reactions is especially pronounced, of course, when dealing with medicinal chemistry, where the biological effects of chemical reactions may be exceedingly difficult to predict from the chemical structure of a compound.")

¹⁴² *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 754 (N.D. W. Va. 2004) ("Of course . . . the prior art suggests that one of the enantiomers is often more active and soluble than its racemate. . . . [T]he prior art certainly indicates that one enantiomer is often more therapeutically active than the other. . . ."); Charlie Lisherness, *Patent Reissue Genus Claims*, 26 T. JEFFERSON L. REV. 85, 87-88 (2003) ("[D]ifferent enantiomers of the same chiral compound can have very different pharmacological properties."); MCMURRY, *supra* note 22, at 323 ("[D]ifferent stereoisomers have . . . dramatically different biological properties.")

¹⁴³ *Hutt & Valentová*, *supra* note 20, at 14-15 ("[I]t is possible that therapeutically useful compounds may have been lost as the racemates were evaluated and thought to be unsuitable for development, whereas their individual enantiomers may have had pharmacologically useful properties.")

¹⁴⁴ *Agranat et al.*, *supra* note 58, at 754.

predict the *in vivo* properties of a hypothetical compound, then an observed property of that compound once it is created may be more likely to be unexpected.

¶51 On the other hand, it is generally accepted that one optical isomer will typically have much higher activity than the other, so that superior activity for at least one of the isomers as compared to the racemate is to be expected.¹⁴⁵ It has therefore been held that differential physiologic activity from one enantiomer to another is not, by itself, unexpected,¹⁴⁶ but that a particular combination of properties may be unexpected.¹⁴⁷

3. Secondary Considerations

¶52 If the improved properties of an enantiomer do not rise to the level of unexpectedness, a second avenue for challenging *prima facie* obviousness is to show the presence of secondary considerations. Secondary considerations, also known as *indicia* of nonobviousness, "must be considered in determining obviousness."¹⁴⁸ Indeed, such objective *indicia* may be "the most probative and cogent evidence in the record"¹⁴⁹ and "alone may defeat a claim of obviousness."¹⁵⁰ Secondary considerations considered by courts to suggest nonobviousness include commercial success,¹⁵¹ long-felt need,¹⁵² failure of others,¹⁵³ copying by competitors,¹⁵⁴ praise by others/industry recognition,¹⁵⁵ industry acquiescence,¹⁵⁶ skepticism by those in the art, and licensing by others. Near simultaneous invention weighs in favor of obviousness.¹⁵⁷

¶53 Commercial success and copying by competitors will almost always weigh in favor of the pharmaceutical patent holder. To establish commercial success, the patentee must merely show significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent.¹⁵⁸ Once this showing is made, it is presumed that the commercial success is due to the patented invention, and the burden then shifts to the other party to show that commercial success is due to other factors.¹⁵⁹

¶54 Normally, a generic company would not challenge a single-enantiomer patent held by a brand name manufacturer unless it wanted to copy the single-enantiomer drug. Not only would the copying itself suggest nonobviousness, but it might also suggest commercial success, a second factor weighing in favor of nonobviousness.¹⁶⁰ Those seeking to invalidate patents on the basis of obviousness have frequently asserted that commercial success is the result of marketing strategy and not the efficacy of the product.¹⁶¹ This assertion is supported by the analysis of the Therapeutics Initiative of the

¹⁴⁵ Carlos M. Correa, *Public Health and Patent Legislation in Developing Countries*, 3 TUL. J. TECH. & INTELL. PROP. 1, 32 (2001).

¹⁴⁶ *In re Adamson*, 275 F.2d 952, 955 (C.C.P.A. 1960).

¹⁴⁷ *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 348 F. Supp. 2d 713, 755 (N.D. W.Va. 2004) ("Although the prior art suggests that [the enantiomer's] relatively higher activity and lower toxicity were not surprising in themselves, the combination of those properties would have been unexpected.")

¹⁴⁸ *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000).

¹⁴⁹ *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

¹⁵⁰ *Ortho-McNeil*, 348 F. Supp. 2d at 749; *but see Newell Co. v. Kennedy Mfg. Co.*, 864 F.2d 757, 768-69 (Fed. Cir. 1988) (stating that "although these factors must be considered, they do not control the obviousness conclusion").

¹⁵¹ *In re Piasecki*, 745 F.2d 1468, 1473, (Fed. Cir. 1984); *Sterling Drug Inc. v. Watson*, 135 F. Supp. 173 (D.D.C. 1955).

¹⁵² *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1539 (Fed. Cir. 1983); *In re May*, 574 F.2d 1082, 1092 (C.C.P.A. 1978).

¹⁵³ *Sterling Drug Inc. v. Watson*, 135 F. Supp. 173 (D.D.C. 1955).

¹⁵⁴ Rebuttal evidence may include evidence that the claimed invention was copied by others. *See, e.g., In re GPAC*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 1380 (Fed. Cir. 1986).

¹⁵⁵ *Brenner v. Ladd*, 247 F. Supp. 51 (D.D.C. 1965).

¹⁵⁶ *Eli Lilly & Co. v. Generix*, 324 F. Supp. 715, 718 (S.D. Fla. 1971), *aff'd* 460 F.2d 1096 (5th Cir. 1972).

¹⁵⁷ *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 753 & 757-58 (N.D. W. Va. 2004).

¹⁵⁸ *Alza Corp. v. Mylan Labs. Inc.*, 388 F. Supp.2d 717, 740 (N.D. W. Va. 2005) (citing *J.T. Eaton & Co. Inc., v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997)) (holding the claimed invention obvious in spite of a finding of "at least moderate commercial success").

¹⁵⁹ *Id.*

¹⁶⁰ *Pfizer Inc. v. Ranbaxy Labs.*, 405 F. Supp. 2d 495, 518 (D. Del. 2005) ("Indeed, the fact that Ranbaxy has chosen to copy Lipitor . . . further demonstrates the success . . . of Lipitor.")

¹⁶¹ *Id.*

University of British Columbia. After evaluating five racemic drugs and their single-enantiomer versions, the Therapeutics Initiative concluded that “[t]he concept that a single enantiomer of a chiral drug may be preferable to a racemic mixture is intellectually appealing. However, in most instances this strategy has not been demonstrated to confer any clinical advantage.”¹⁶² Importantly, it was noted that while single-enantiomer drugs may be more effective at the same dosage level, clinical equivalence can be achieved by simply increasing the dosage level of the racemic drug.¹⁶³ Courts, however, have not always agreed.¹⁶⁴ Nor is there consensus among commentators, with some suggesting that single enantiomers are clearly better,¹⁶⁵ and others suggesting that even if enantiomers have “clear clinical advantages over racemates” in some cases,¹⁶⁶ the market success of single-enantiomer drugs is really “based more on promotion than on real advantages.”¹⁶⁷ Whether the result of marketing or superior properties, the percentage of new drugs that are single enantiomers has increased from 20% to 75% in a recent ten-year period.¹⁶⁸

¶55

Even if commercial success is due to promotion rather than the merits of the product, a defendant attempting to prove this to the court faces a particularly difficult challenge. On the one hand, it must assert that the enantiomer is not significantly better than the racemate. This is because if the enantiomer were significantly better, this would tend to show that commercial success was due to the superior qualities of the product rather than marketing efforts. Yet if the generic company’s assertion is true, then a court will naturally wonder why the generic company has not copied the unpatented racemate rather than the patented enantiomer.¹⁶⁹

4. No Known or Obvious Process

¶56

Even if a prima facie case of obviousness is established, and no unexpected results can be shown nor favorable secondary considerations relied upon, an enantiomer may nevertheless be nonobvious if no method of resolution is disclosed in or rendered obvious by the prior art. “One of the assumptions underlying a prima facie obviousness rejection based upon a structural relationship between compounds . . . is that a method disclosed for producing one would provide those skilled in the art with a method for producing the other.”¹⁷⁰ Due to the fact that enantiomers have identical chemical (but not biological) properties, the process for making the racemate may not make obvious a process for resolving the racemate. Even if the prior art discloses a process for isolating one enantiomer, this process will not necessarily render obvious the process for obtaining the other enantiomer.¹⁷¹

[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

¹⁶² *Do Single Stereoisomer Drugs Provide Value?*, *supra* note 14; Blin, *supra* note 66, at 625, 627 (concluding that demonstrating improved clinical effectiveness for single-enantiomer drugs over their racemates has proven difficult in most cases).

¹⁶³ *Id.*

¹⁶⁴ *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 757 (N.D. W. Va. 2004) (“[T]he evidence reflects a fairly extensive recognition among doctors and hospitals that levofloxacin is not only an effective drug but also is clinically distinguishable from ofloxacin.”). Note that levofloxacin was one of the enantiomers evaluated by the Therapeutics Initiative. *Do Single Stereoisomer Drugs Provide Value?*, *supra* note 14.

¹⁶⁵ Agranat et al., *supra* note 58, at 754 (“The debate about the relative merits of racemates and single enantiomers was short lasting, and it was resolved emphatically in favour of the latter.”); *see also* Hutt & Valentová, *supra* note 20, at 10 (noting that racemic penicillamine resulted in optic neuritis and was withdrawn from the US market, while the use of D-penicillamine [the single enantiomer] was not observed to cause the adverse side effect; also noting the use of single-enantiomer L-dopa in the treatment of Parkinson’s disease resulted in reduced adverse effects as compared to the racemate).

¹⁶⁶ Mansfield et al., *supra* note 29, at 287-88.

¹⁶⁷ *Id.* at 290.

¹⁶⁸ Agranat et al., *supra* note 58, at 753.

¹⁶⁹ *See, e.g., Ortho-McNeil*, 348 F. Supp. 2d at 759 (“Notwithstanding the expiration of the [racemate] patent and [the defendant’s] insistence that [the racemate] and [the enantiomer] are virtually indistinguishable, [the defendant] chose to file an ANDA only for [the enantiomer].”).

¹⁷⁰ *In re Grose*, 592 F.2d 1161, 1168 (C.C.P.A. 1979).

¹⁷¹ *Brenner v. Ladd*, 247 F. Supp. 51, 55 (D.D.C. 1965).

a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious. . . .¹⁷²

¶57 Consider this matter from the perspective of motivation to combine and reasonable likelihood of success. The mere disclosure in the prior art of a racemate and a resolution technique does not mean that the given racemate will be amenable to resolution by the given technique. There must be more than a general motivation to resolve a racemate; there must be a motivation to combine particular references with each other. That is, there must be a suggestion from the prior art that a particular racemate can be resolved by a particular technique with a reasonable expectation of success.

CONCLUSION

¶58 Within the law of chemical obviousness, enantiomers present a special case. A disclosed racemate allows one ordinarily skilled in the art to envision the structure of each enantiomer. Given this racemate, the ordinarily skilled worker does not need to select a single molecule from hundreds or thousands of unique molecules that might be imagined by arranging numerous substituents in myriad ways. There are only two species within the genus. The pharmaceutically active racemate is already known to be useful, and the literature is replete with the potential advantages of single-enantiomer drugs over their racemates. One skilled in the art would therefore generally have a motivation to resolve a racemate in the ever-present search for superior pharmaceutical products. True, many single enantiomers have failed to demonstrate improved clinical properties, but while this clearly demonstrates the lack of absolute predictability, it does not necessarily negate a reasonable expectation of success. With advances in separation techniques, the likelihood of success in obtaining a single enantiomer has increased, and the existence of potential benefits has been acknowledged by the FDA's call for single-enantiomer data during the drug approval process. Moreover, the case of enantiomers seems to fall squarely within the circumstances aptly articulated by the Fifth Circuit:

[W]here a court finds the alleged inventor's work in a field filled with formidable prior art to be no more novel or nonobvious than the conducting of a biological or physiological testing program among catalogued compounds or an easily formulated series of homologues or analogues that logically or predictably should disclose helpful uses, the grant or validation of a patent on the product would be out of keeping with the letter or spirit of the law.¹⁷³

¶59 All of this, of course, is merely a general approach to addressing the patentability of enantiomers. Ultimately “[e]very case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts.”¹⁷⁴ Enantiomers may merit patent protection in certain circumstances. For example, if a racemate is disclosed but has no known uses, one skilled in the art would not possess the requisite motivation or likelihood of success. Or if the racemate was disclosed to be highly toxic this could constitute “teaching away” so as to favor nonobviousness. Or perhaps the single enantiomer possesses properties so different in kind or magnitude that they would have been totally unexpected to one skilled in the art.

¶60 Ultimately, the determination of whether and when enantiomers should be patentable is a public policy question and should be addressed with this in mind. Single-enantiomer drugs have in some cases been shown to be superior to their racemates. At the same time “[t]here are . . . financial risks associated with the development of single enantiomers from racemates.”¹⁷⁵ To the extent that such

¹⁷² *In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968); *In re Payne*, 606 F.2d 303, 314-15 (C.C.P.A. 1979) (“[T]he presumption of obviousness based on close structural similarity is overcome where the prior art does not disclose or render obvious a method for making the claimed compound.”); *In re Maloney*, 411 F.2d 1321, 1323 (C.C.P.A. 1969) (“[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.”). *Acord Emory Univ. v. Glaxo Wellcome Inc.*, 44 U.S.P.Q.2d 1407, at *9 (N.D. Georgia 1997).

¹⁷³ *Eli Lilly & Co. v. Generix*, 460 F.2d 1096, 1103 (5th Cir. 1972).

¹⁷⁴ *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992).

¹⁷⁵ *Hutt & Valentova*, *supra* note 20, at 16; *Blin*, *supra* note 66, at 625 (emphasizing the scientific, administrative, and economic challenges surrounding the commercial development of single-enantiomer drugs).

financial risks deter companies from developing single-enantiomer drugs, offering patent protection for those single enantiomers that offer true advantages would both serve the public interest and fulfill the Constitutional objective of promoting the progress of science.