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TARGETING ENANTIOMER PRODUCT HOPPING WITH A NEW "OBVIOUSNESS" STANDARD

Mark Metzke

In the pharmaceutical industry, product hopping may occur in the patenting of a purified enantiomer after the patenting of its parent racemate. By product hopping, a brand name manufacturer delays generic competition and maintains market exclusivity. This delay results in higher product costs to patients, harming the public and conflicting with the core utilitarian goals of the patent system. This Note proposes several changes to the obviousness doctrine to better prevent brand name manufacturers from product hopping. By establishing prima facie obviousness as given, changing what courts may consider an "unexpected result," and adjusting the secondary considerations courts consider in patent cases, some of the most problematic forms of enantiomer product hopping can be eliminated.

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I. INTRODUCTION

Enantiomer patenting can be, and arguably has been, manipulated to allow unjustified extensions of market exclusivity. These extensions occur when a purified enantiomer is patented at some time after the patenting of its parent racemate. In cases where there is little clinical gain in using the resolved enantiomer, the later patent may harm the public by allowing a brand name prescription holder to "product hop" to a different pharmaceutical formulation.[1] This "hop" staves off generic competition, maintains market exclusivity, and results in higher product costs to patients. This Note examines the current doctrine concerning the patenting of enantiomers. It then addresses problems associated with enantiomer-based product hopping by proposing a modified patent doctrine.

Though many of the current patenting standards surrounding enantiomers work effectively, some parts of this doctrine can be tweaked to better eliminate product hopping. This

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[1] In this Note, "brand name manufactures" will be an umbrella term referring to companies primarily concerned with patenting new pharmaceutical compounds.

Note proposes changes to "obviousness" standards to better deny strategic patents. By establishing prima facie obviousness as given, clearly defining what constitutes an "unexpected" result, and adjusting the secondary considerations used to rebut obviousness,[2] courts will have a better chance to weed out enantiomer product hopping. Following this brief introduction, Part II of this Note describes pharmaceutical patenting incentives and, briefly, the chemistry behind racemates and enantiomers. The specific product hop from omeprazole to (-)-omeprazole is then described. Part III discusses the law behind enantiomer patenting and elucidates current obviousness standards. Part IV proposes a new obviousness standard, better suited to invalidate product hopping patents. This new doctrine is applied to two case studies, one involving the patenting of omeprazole and the other floxacin.[3] Part V concludes.

II. THE BIG-PICTURE: ENANTIOMERS AND PRODUCT HOPPING

a. Pharmaceutical Patenting

The pharmaceutical industry depends on the patent system to protect its intellectual property for marketed drugs.[4] Once marketed, active pharmaceutical ingredients ("APIs") are in the public domain and are readily accessible to competitors. In accordance with the FDA's regulatory framework governing the safety and efficacy of a drug, a certain level of public disclosure is necessary for clinical approval of APIs.[5] But for patent protection, APIs could be isolated, characterized, and synthesized by competitors. Competitors could bring their version of a drug to market at a fraction of the cost, with little risk of FDA rejection, allowing them to free

[2] This "adjusting" would guide patent examiners and courts to make *only relevant* therapeutic comparisons. *See infra* Part IV (defining "relevant").
[3] Both of these drugs were disclosed prior to the patenting of their resolved enantiomers. These drugs will be analyzed as though they were undergoing a patent validity challenge.
[4] *See* Michael H. Brodowski et al., *Managing Innovation: Patent Basics for Biotechnology Counsel*, *in* BIOTECHNOLOGY AND THE LAW 25, 25 (Hugh B. Wellons et al. eds., 2007).
[5] *See* Miles J. Sweet, *The Patentability of Chiral Drugs Post-KSR: the More Things Change, the More They Stay the Same*, 24 BERKELEY TECH. L. J. 129, 129 (2009).

ride on the research efforts of brand-name manufacturers.[6]

To combat free riding and to incentivize public disclosure and innovation, the government offers innovators an approximately 20 year monopoly on their inventions, in the form of a patent.[7] This monopoly can ultimately lead to enormous financial success for pharmaceutical innovations.[8] As such, the patent system has been lauded as a great success story for pharmaceuticals.[9]

When a patent expires, however, the monopoly is lost and competing companies may synthesize generic equivalents of APIs without threat of infringement.[10] Generic equivalents undergo an abbreviated FDA approval process and enter the market at vastly reduced costs of production. Part of this reduced cost is passed on to the customer.[11] Generic competition drives the market price of drugs down and can cause the brand name manufacturer's revenue to decrease by billions of dollars.[12] Thus, prolonging patent life is in the best interest of brand name pharmaceutical producers. One strategy to prolong patent life is to product hop.[13]

In product hopping, a brand name manufacturer makes a minimal change or insignificant improvement to its API. Then, the manufacturer attempts to patent and market this new product

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[6] *See* Areta L. Kupchyk, *Approval of Products for Human Use*, *in* BIOTECHNOLOGY AND THE LAW, 603-6 (Hugh B. Wellons et al., eds., ABA Publishing, 2007) [Hereinafter *Kupchyk*].
[7] Brodowski, *supra* note 4, at 27.
[8] *See generally* Drugs.com, Top 200 Drugs for 2008 by Sales, http://www.drugs.com/top200.html (last visited May 29, 2010).
[9] *See* Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 504 (2009); *see also* Drugs.com, *supra* note 8 (indicating the 34 top selling drugs each earn over a billion dollars in revenue each year). *But see Billion Dollar Pills*, ECONOMIST, Jan. 27, 2007, at 69 (explaining that experts estimate it takes close to $500 million to $2 billion to bring a new drug to market). So, even with the patent system in place, the financial successes of pharmaceuticals are tempered by enormous financial risk that comes in the R&D and testing of a drug. Additionally, only a small percentage of drugs that enter clinical trials will ever gain entry to the market.
[10] Kupchyk, *supra* note 6, at 603.
[11] This is a benefit for the public at large. The government is in constant tension between the need to protect IP enough to incentivize investment, while not protecting it so much that the consumer is hurt unnecessarily. *See* Gardiner Harris, *Prilosec's Maker Switches Users To Nexium, Thwarting Generics*, WALL ST. J., June 6, 2002, at A1, *available at* http://www.chelationtherapyonline.com/technical/p36.htm.
[12] *See* Jessie Cheng, *An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry*, 108 COLUM. L. REV. 1471, at 1471 (2008) (giving an excellent overview of several products suspected of product-hopping).
[13] *Id.* at 1472.

commercially.[14] Once the new product is on the market, the brand name manufacturer may pull the product with the expiring patent off the shelves. Then prescriptions can be filled using the new product that has an extended patent life, instead of the product with an expiring patent. Because generic drug providers must provide physicians with "generic equivalents," the new product formulation prevents the generic provider from entering the market until the new patent expires.[15]

b. Racemates and Their Component Enantiomers

One area of pharmaceutical chemistry uniquely susceptible to product hopping is in the patenting of enantiomers resolved from their racemates.[16] A racemate, or racemic mixture, consists of exactly two stereoisomers called enantiomers.[17] Coinciding enantiomers have the same molecular formula, connectivity,[18] and chemical and physical properties.[19] However, enantiomers are different three-dimensionally. Like your left hand and your right hand, enantiomers are non-superimposable mirror images of each other. Each enantiomer has its own "handedness" and is designated "(+)" or "(-)" depending on the orientation of substituents in space.[20] Because of their different spacial arrangement, (+) and (-)-enantiomers *may* have different biological activities.[21] For example, the (+)-enantiomer could have higher clinical efficacy than the corresponding (-)-enantiomer.[22] Still, other enantiomers may have nearly equivalent biological properties. The

[14] *Id.*
[15] *Id.* at 1494. This patent prolonging strategy was described as a "thinly disguised scheme to game the pharmaceutical industry's regulatory system." *Id.* (referring to the FDA approval process and the patenting process as the "regulatory system").
[16] Resolved, or resolution is just the purification of an enantiomer from the parent racemate.
[17] This mixture of compounds happens as a byproduct of asymmetric chemical synthesis.
[18] Each substituent group is connected to the same atom when comparing the enantiomers. *See* SEYHAN N. EĞE, ORGANIC CHEMISTRY: STRUCTURE AND REACTIVITY 198 (Richard Stratton et al. eds., 4th ed. 1999).
[19] *Id*. at 198-99. Because they have identical physical and chemical properties, resolving an enantiomer from the racemate can be difficult and costly. Therefore, patenting the racemate is an attractive alternative to resolution.
[20] This "(-)" or "(+)" designation indicates the direction in which plane polarized light is rotated when passed through the enantiomer and (±) constitutes the racemate. *See generally* EĞE, *supra* note 18, at 198.
[21] Sometimes only the (+) or (-)-enantiomer will fit into the active site of an enzyme, protein, or other biological structure.
[22] *See generally* Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, STAN. TECH. L. REV., Feb. 27, 2007, ¶¶ 5-11 (discussing the different properties of enantiomers, giving an

isolation of enantiomers that have no clinical advantage over their racemic mixture is substantively irrelevant.[23]

An issue then arises when a resolved enantiomer that offers little clinical improvement over its racemate is patented at the end of its parent racemate's patent term. This patenting just prolongs the patent monopoly and constitutes a product hop. Racemates are especially attractive for product hopping because the risk of FDA rejection for a component enantiomer of a previously approved racemate pharmaceutical is low.[24] Also, the racemate patent holder understands that at least one of the enantiomers is likely therapeutically active; thus, the racemate patent holder need only resolve the enantiomer to be granted another patent monopoly. This is a much more attractive alternative to developing a wholly new API or an analog that may be synthetically challenging.

c. Product Hopping: Omeprazole to Esomeprazole

A product hopping patenting strategy may have been used in AstraZeneca's later patenting of (-)-omeprazole[25] over (±)-omeprazole,[26] (Figure 1). Prilosec is a racemic version of omeprazole and Nexium is the single (-)-omeprazole enantiomer. Prilosec and Nexium have the therapeutic effect of lowering the acidity in the stomach through deactivation of proton pumps. Both drugs

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excellent review of the obviousness doctrine as it pertains to enantiomers, and offering many good insights); John Caldwell, *Do Single Enantiomers Have Something Special to Offer?*, 16 HUMAN PSYCHOPHARMACOLOGY S67, S67-S71 (2001) (discussing the improved "benefit-risk" profile of some single enantiomers, and that some single enantiomers may have no therapeutic improvement over the enantiomer); Vijay V. Moghe et al., *Thalidomide*, 50 BOMBAY HOSPITAL JOURNAL 472, 472-76 (discussing the conversion of enantiomerically pure thalidomide to both the *R* and *S* enantiomers under biological conditions). As stated in the Moghe article, one of these enantiomers is responsible for lower the effect of morning sickness in pregnant women and is a mild sedative. The other enantiomer is a teratogen and can produce birth defects in children. Because these enantiomers interconvert at physiological pH, administering one the non-teratogenic enantiomer will not prevent the teratogen from entering the body.

[23] Caldwell, *supra* note 22, at S68.

[24] The compound has already undergone FDA approval as the racemate.

[25] The brand name of this compound is Nexium. Esomeprazole is also a conventional name along with (-)-omeprazole.

[26] The brand name of this compound is Prilosec. This is referred to as 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole.

are proton-pump inhibitors ("PPIs") used in the treatment of gastroesophageal reflux disease (GERD), which causes heartburn, irritates ulcers, and is associated with erosive esophagitis.[27]

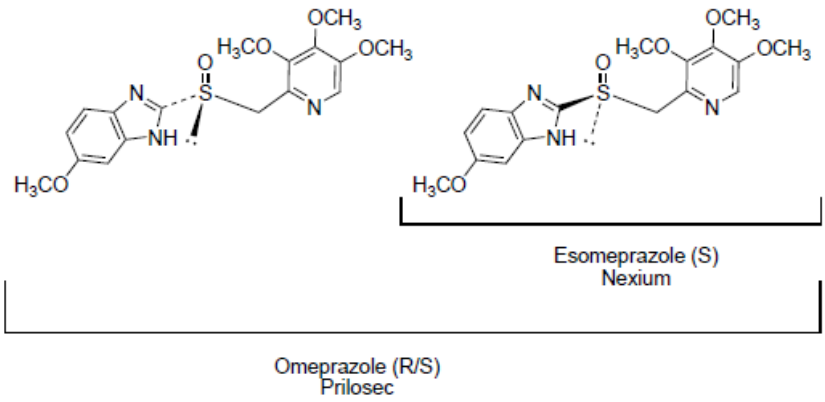

Figure 1. The mixture of the (+) and (-)-enantiomers yield omeprazole, the API of Prilosec. The (-)-enantiomer alone gives esomeprazole, the API of Nexium.

In 2000 alone, Prilosec earned an estimated $6 billion.[28] AstraZeneca's patent for this tremendously successful drug was due to expire in April 2001.[29] This pending expiration spurred AstraZeneca to initiate the "Shark Fin Project."[30] This project was an attempt to breathe new life into the expiring monopoly.[31] Just one month before the Prilosec patent expired, AstraZeneca

[27] *See generally* Nexium Research, Esomeprazole and GERD, http://www.nexiumresearch.com/ (last visited May 29, 2010). The omeprazole molecule covalently bonds to H,K ATPase enzyme of parietal cells in the stomach. This bonding causes an irreversible blockage of the "proton pump" of a cell (one molecule of a "proton pump inhibitor" blocks one equivalent pump), but only the *S* isomer fits into the active site of the enzyme. U.S. Patent No. 5,877,192 (filed Apr. 11, 1997).
[28] *See* ASTRAZENECA, ANNUAL REPORT & FORM 20-F 2000, at 38 (2001) (reporting $6.3 billion from gastrointestinal drugs in 2000); *see also* Harris, *supra* note 11 (estimating $26 billion in sales in five years for Prilosec in 2002).
[29] *See* Harris, *supra* note 11; *see also* Malcolm Gladwell, *High Prices: How to Think About Prescription Drugs*, NEW YORKER, Oct. 25, 2004, at 86.
[30] Gladwell, *supra* note 29.
[31] Cheng, *supra* note 12, at 1490; *see also* Gladwell, *supra* note 29 (stating that a 90% healing rate with Nexium was patentable over the 87% healing rate of Prilosec).

released a new patented formulation—Nexium.[32] Nexium was simply the resolved (-) isomer of omeprazole. Because of the release of Nexium, AstraZeneca was able to extend its exclusivity until May 2014.[33] Nexium boasted $4.8 billion in sales last year alone.[34]

d. Targeting the Nexium Product Hop in Court

In challenging AstraZeneca under antitrust law, the Walgreen Company asserted "AstraZeneca's product-switching from Prilosec to Nexium was profitable for AstraZeneca only because the strategy had the effect of impairing generic competition to Prilosec. Absent that effect, engaging in the product switch would have made no economic sense for AstraZeneca."[35] AstraZeneca's product hop denied generics from becoming widely available at a lower cost to consumers. The Walgreen Company's antitrust challenge was unsuccessful though.[36]

A different way to attack product hopping, once outside the realm of antitrust, is to challenge the validity of the patent itself. This Note lays out a framework for targeting product hopping. In attempting to defeat a product hopper's patent, the attack focuses on the claimed compound's obviousness.[37] With some subtle adjustments to the obviousness doctrine, product hoppers can better be denied patents. The rationale follows in Part IV.

III. CURRENT DOCTRINE REGARDING OBVIOUSNESS

a. Patentability Overview

[32] Gladwell, *supra* note 29.
[33] *See* Press Release, AstraZeneca, AstraZeneca Settles US Nexium Patent Litigation with Ranbaxy (Apr. 15, 2008), http://www.astrazeneca.com/media/latest-press-releases/2008/5387?itemId=3892250.
[34] *See* Drugs.com, *supra* note 8.
[35] First Amended Complaint and Demand for Jury Trial at 15, Walgreen Co. v. AstraZeneca Pharms., 534 F. Supp. 2d 146 (D.D.C. 2008) (No. 1:06 CV 02084-RWR); *see also* Darrow, *supra* note 22, ¶¶ 5-11 ("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.").
[36] Walgreen Co. v. AstraZeneca Pharms., 534 F. Supp. 2d 146 (D.D.C. 2008).
[37] Novelty would also seem to be a target. *But see In re* Williams, 171 F.2d 319, 320 (C.C.P.A. 1948) (holding "[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 . . . render the claim unpatentable for [obviousness]").

To be awarded a patent, an invention must have utility,[38] be novel,[39] be non-obvious,[40] and it must be enabled.[41] Section 103 of the Patent Act articulates the "non-obviousness" requirement, stating that an invention is patentable unless "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been *obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains*."[42] In *Graham v. John Deere Co.*, the U.S. Supreme Court laid out a four factor analysis for determining non-obviousness.[43] The *Graham* obviousness factors include: (1) the level of ordinary skill in the art, (2) the scope and content of the prior art, (3) the differences between the claimed invention and the prior art, and (4) certain secondary considerations.[44] Then, "[a]gainst this background, the obviousness or non-obviousness of the subject matter is determined."[45]

Obviousness is distinct from prima facie obviousness in pharmaceutical patenting. To establish prima facie obviousness, a patent challenger[46] uses the first three *Graham* factors. If prima facie obviousness can be established by the patent challenger, the burden of proof shifts from the patent challenger to the patent holder.[47] The patent holder then has the opportunity to rebut the obviousness claim by showing secondary considerations exist, as mentioned in the

[38] 35 U.S.C. § 101 (2006).
[39] 35 U.S.C. § 102 (2006).
[40] 35 U.S.C. § 103 (2006).
[41] 35 U.S.C. § 112 (2006).
[42] 35 U.S.C. § 103 (emphasis added).
[43] Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966).
[44] *Id.*
[45] *Id.* at 17.
[46] Or the patent examiner.
[47] *See* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1360 (Fed. Cir. 2007) ("It is true that once a challenger has presented a prima facie case of invalidity, the patentee has the burden of going forward with rebuttal evidence . . . . But, all that means is that even though a patentee never must submit evidence to support a conclusion by a judge or jury that a patent remains valid, once a challenger introduces evidence that might lead to a conclusion of invalidity-what we call a prima facie case-the patentee 'would be well advised to introduce evidence sufficient to rebut that of the challenger.'" (citations omitted)).

fourth *Graham* factor.[48] If the patent applicant cannot rebut the claim, then obviousness is grounds for invalidating the patent.

b. Establishing Prima Facie Obviousness

i. The POSITA

The prima facie obviousness inquiry begins by defining a person of ordinary skill in the art ("POSITA"). The Manual of Patent Examining Procedure has determined that a POSITA "is a hypothetical person who is presumed to have known the relevant art at the time of the invention."[49] The factors to assess ordinary skill include the: "(A) 'type of problems encountered in the art;' (B) 'prior art solutions to those problems;' (C) 'rapidity with which innovations are made;' (D) 'sophistication of the technology; and' (E) 'educational level of active workers in the field.'"[50] This is a time-sensitive inquiry. Therefore, as more is learned about enantiomers over time, the more the POSITA knows and the more obvious enantiomer isolation and separation becomes. For pharmaceutical chemistry, the POSITA would likely be a person with an advanced degree who is trained in synthetic chemistry.[51]

ii. "Scope and Content of the Prior Art"

A. Suggestion and Motivation

Next, courts will address the "scope and content of the prior art" *Graham* factor. This analysis is known as the teaching, suggestion, motivation ("TSM") test. In this test, a claim is

[48] The analysis is somewhat modified for enantiomers, as rebuttal evidence showing unexpected results or a non-obvious resolution technique can also weigh in favor of the patent holder, or patent applicant.
[49] U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE 2100-18 (8th ed. 2001) (citations omitted).
[50] *Id.*
[51] *See* Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 750 (N.D. W. Va. 2004) (defining a POSITA as someone with "an advanced degree (though not necessarily a doctorate) in chemistry or a related discipline, which included the study of stereochemistry," and noting that "[a] skilled artisan also would have had either (a) substantial laboratory or clinical experience in pharmaceutical research and development or (b) substantial familiarity with principles of pharmacology and pharmaceutical synthesis").

obvious if "some motivation or suggestion to combine the prior art teachings" can be found.[52] The recent decision in *KSR v. Teleflex* encouraged a flexible approach in determining obviousness[53] and further concluded that "obvious to try" may lead to a finding of obviousness despite what previous courts had held.[54] Whether *KSR* has actually changed the test for pharmaceutical obviousness is not yet apparent,[55] but *KSR* could serve as a basis for changes in analyzing enantiomers.

In the case of enantiomers, it is well understood certain molecular features give rise to stereocenters and therefore racemic mixtures.[56] So, the very existence of a stereocenter makes the existence of an enantiomeric pair obvious. Also, many enantiomer separation techniques have been disclosed and are widely available in the chemical industry. There exist several references suggesting the benefits of separating racemic components to lower side-effects and to improve efficacy.[57] The question that arises is whether this generalized knowledge would lead to motivation of the POSITA inherently to separate enantiomers.

In some instances, courts have determined that the generalized knowledge of improved

[52] Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1323-24 (Fed. Cir. 1999).
[53] *See* KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 415 (2007) ("We begin by rejecting the rigid approach of the Court of Appeals. Throughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach inconsistent with the way the Court of Appeals applied its TSM test here. To be sure, *Graham* recognized the need for 'uniformity and definiteness.' Yet the principles laid down in *Graham* reaffirmed the "functional approach" of *Hotchkiss*. To this end, *Graham* set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive." (citations omitted)).
[54] *See id.* at 402-03 ("[T]he court erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.").
[55] *See* Jonathan M. Spenner, *Obvious-to-Try Obviousness of Chemical Enantiomers in View of Pre- and Post-*KSR *Analysis*, 90 J. PAT. & TRADEMARK OFF. SOC'Y 475, 500 (2008) ("[T]he Supreme Court was simply telling the Federal Circuit to follow its own precedent."). *But see* Janice M. Mueller, *Chemicals, Combinations, and "Common Sense": How the Supreme Court's* KSR *Decision is Changing Federal Circuit Obviousness Determinations in Pharmaceutical and Biotechnology Cases*, 35 N. KY. L. REV. 281, 308 (2008) ("After KSR, it is unquestionably easier to establish a prima facie case of obviousness in the chemical arts.").
[56] Quaternary carbons and sulfoxides are two examples. *See generally* EĞE, *supra* note 18, at 193.
[57] *See* Peter Mansfield et al., *Single Enantiomer Drugs: Elegant Science, Disappointing Effects*, 43 CLINICAL PHARMACOKINETICS 287, 287 (2004).

properties of enantiomers over their racemate, in light of disclosed separation techniques, gives the POSITA inherent motivation to resolve the racemate.[58] But this holding varies from case to case, because the relevant timeframe of the initial conception changes. As late as 1991, a federal court found that the disclosure of a racemate did not provide motivation for the separation and taught away from the separation in some instances.[59] When the prior art "teaches away from" a particular finding, this pushes against a finding of motivation.[60]

B. Reasonable Expectation of Success

Motivation also requires that the POSITA have at least a "reasonable expectation of success" when combining prior art references.[61] In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, the court applied reasoning from *Yamanouchi Pharmaceutical Co., Ltd. v. Danbury Pharmacal, Inc.*, necessitating "prior art . . . not only motivate a person of ordinary skill in the art to make [the API] but also reasonably suggest that the compound would exhibit its

[58] *See, e.g.*, Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 752 (N.D. W. Va. 2004) (statement of Dr. Isao Hayakawa) ("'With 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 one is, if bluntly said, almost an impure substance. Influenced by ideas like these, we decided to focus on the antibacterial activity of the two enantiomers, resulting in the application of optical resolution.'" (citation omitted)); *see also In re* Adamson, 275 F.2d 952, 952 (C.C.P.A. 1960) (Specific racemates do not need to be disclosed because "[t]he fundamentals of optical activity and stereo-isomerism are presented in a section of an organic chemistry text written by Karrer. Principally relied upon by the Patent Office are the teachings therein that optical activity is attributable to asymmetric molecular structure and that synthetically produced substances containing asymmetric carbon atoms are optically inactive due to the formation of equal amounts of the dextro- and laevo-isomers. Such compounds are said to be racemic. Karrer teaches that racemates may be resolved (separated) by various methods including the one utilized by appellants to separate their specific laevo-isomers."). The *In re Adamson* case is also relevant because it sets precedent for motivation coming from one reference and not the combining of two references. *See generally* Darrow, *supra* note 22, ¶ 22 (providing more discussion on this topic).

[59] *See* Pfizer Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495, 517 (D. Del. 2005) ("This modest [two-fold] increase in activity was offset by the difficulty and complexity of the resolution process, as well as the reduced yield and increased waste disposal problems.").

[60] In *Ranbaxy Laboratories Ltd.*, 405 F. Supp. 2d 495, the court found that when a reference "teach[es] away from" a particular outcome, that outcome can be used to establish non-obviousness. In *Ranbaxy Laboratories Ltd.*, knowledge of the POSITA as late as 1991, did not establish motivation to resolve an enantiomer. Because enantiomer separations were difficult to perform during the relevant time frame, the disclosure of these racemates taught toward synthesizing new analogs or compounds rather than resolving the enantiomers.

[61] Alza Corp. v. Mylan Labs. Inc., 388 F. Supp. 2d 717, 737 (N.D. W. Va. 2005) (citing *In re* O'Farrell, 853 F.2d 894, 904 (Fed. Cir. 1988)).

unique combination of properties."[62] The hurdle for finding an enantiomer obvious seems extremely high, because even if some properties of the new API are predictable, certain aspects of a compound can never be known until it is synthesized.[63]

However, as the *In re Dillon* court pointed out and Jonathan J. Darrow explains, this standard is not to be followed strictly and it should be enough that the compound possesses one predictably improved property.[64] *In re O'Farrell* added that, in prima facie obviousness, "absolute predictability of success" is not required.[65] The expectation of success pertains not only to the predictability of the properties, but also to the preparation of the compound. Therefore, there must be some expectation of success in the separation of an enantiomer under the current standard.

iii. The Differences Between the Claimed Invention and the Prior Art

A. Structural Similarities between Claimed and Prior Art Compounds

For a chemical compound the prima facie case also "requires 'structural similarity between claimed and prior art subject matter.'"[66] The *In re Payne* court qualified this statement, adding that when obviousness is based on motivation and similarity in chemical structure, there is an "expectation that compounds similar in structure will have similar properties."[67] This expectation implies that similar compounds with different properties may be non-obvious.[68]

B. Genus Size of Prior Art Compounds

When deciding the obviousness of a compound previously disclosed in the prior art, the

[62] *Ortho-McNeil Pharm., Inc.*, 348 F. Supp. 2d at 749 (citing Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1345 (Fed. Cir. 2000)).
[63] For example, melting point, solubility, etc.
[64] *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."); *see also* Darrow, *supra* note 22, ¶ 36.
[65] *In re* O'Farrell, 853 F.2d at 903; *see also Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d at 517.
[66] *Yamanouchi Pharm. Co.*, 231 F.3d at 1343 (quoting *In re* Dillon, 919 F.2d at 692).
[67] *In re* Payne, 606 F.2d 303, 313 (C.C.P.A. 1979).
[68] *See* discussion *infra* Part III.c.

size of the genus from which the previously disclosed compound comes may also be a factor.[69] If the genus is very small, the likelihood of an obviousness finding increases, though genus size may not be dispositive.[70] A racemate consists of exactly two enantiomers forming the smallest possible genus. This small genus weighs toward prima facie obviousness.

iv. Summary of Prima Facie Obviousness

In view of the previous factors, it may seem that prima facie obviousness is de facto established for enantiomers.[71] In fact, several courts have articulated just that conclusion.[72] However, courts as recently as 2004 have refused to accept such a generalized finding.[73] The Board of Patent Appeals has reiterated that disclosure of an enantiomer alone does not create a case of prima facie obviousness.[74] It is also important to acknowledge that a new separation technique alone may defeat prima facie obviousness.[75] Separations are discovered and disclosed

[69] Darrow, *supra* note 22, ¶ 26; *see also* Spenner, *supra* note 55, at 500-01.
[70] Guidelines for the Examination of Claims Directed to Species of Chemical Compositions Based Upon a Single Prior Art Reference, 63 Fed. Reg. 47000, 47002 (Sept. 3, 1998) ("The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. A proper obviousness analysis involves a three step process. First, Office personnel should establish a prima facie case of unpatentability considering the factors set out by the Supreme Court in *Graham v. John Deere*. If a *prima facie* case is established, the burden shifts to applicant to come forward with rebuttal evidence or argument to overcome the prima facie case. Finally, Office personnel should evaluate the totality of the facts and all of the evidence to determine whether they still support a conclusion that the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made.").
[71] *See In re* Jones, 958 F.2d 347, 349-50 (Fed. Cir. 1992) (citations omitted).
[72] *See, e.g.*, Brenner v. Ladd, 247 F. Supp. 51, 56 (D.D.C. 1965) ("This Court agrees . . . that, in the absence of unexpected or unobvious beneficial properties, an optically active isomer is unpatentable over either the isomer of opposite rotation or, as in this case, the racemic compound itself." (citations omitted)); Sterling Drug Inc. v. Watson, 135 F.Supp. 173, 175 (D.D.C. 1955) ("[U]nless a verified showing is made that the claimed compounds possess unexpected or unobvious beneficial properties not possessed by the homologous (or isomeric) compound of the prior art, and which properties differ in kind from the properties of the prior art compound, the claimed compounds do not involve invention over the prior art compound.").
[73] Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 749 n.19 (N.D. W. Va. 2004) ("Mylan asserts that enantiomers are prima facie obvious vis-a-vis the racemic compound. Although *Jones* and *May* support Mylan's contention, they are inconsistent with the Federal Circuit's directive to make *Graham* findings in *every* case to establish a prima facie case of obviousness." (citing *In re* Jones, 958 F.2d at 350 (citing *In re* May, 574 F.2d 1082 (C.C.P.A. 1978))).
[74] *Ex parte* Bonfils, 64 U.S.P.Q.2d 1456, 15-16 (B.P.A.I. 2002).
[75] *See* Emory Univ. v. Glaxo Wellcome Inc., 44 U.S.P.Q.2d 1407, 1414 (N.D. Ga. 1997) ("[D]isclosure of the racemate . . . makes prima facie obvious the separate enantiomers of that racemate" but that the separation must also be obvious.").

over time. If a patent makes use of a separation technique that has not been disclosed or that is not obvious in light of the combination of references, then prima facie obviousness will not be established. Therefore, case to case analysis is still necessary.

c. Rebutting Prima Facie Obviousness

i. Unexpected Improvement in Results

In re Soni indicated that "[w]hen a chemical composition is [prima facie obvious] . . . the presumption [is] that *similar compositions have similar properties*."[76] The implication is that when the enantiomer has improved properties over the racemic mixture, such as efficacy, lower side effects, or improved solubility, a prima facie showing of obviousness can be overcome.[77] In the case of a single improved property, courts have suggested "an unexpected result must be a *substantial* improvement over the prior art."[78] For an API already marketed as a racemate, the level of pharmacological activity may be the most relevant difference.[79] An increase in activity by several times has in some cases led to findings of non-obviousness by itself.[80] However, if the prior art predicts improvement in drug properties, the relevant comparison becomes the actual

[76] *In re* Soni, 54 F.3d 746, 750 (1995) (emphasis added) (citations omitted); *see also 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, and thus the prima facie case of obviousness, rises from the expectation that compounds similar in structure will have similar properties." (citations omitted)); *In re* Grabiak, 769 F.2d 729 at 731 (1985) ("'[V]ery close' structural similarities and similar utilities, *without more* a *prima facie* case may be made." (emphasis added) (citations omitted)). In *In re Grabiak*, this "'very close' structural similarity and similar utilities, without more" seems to indicate that other properties are taken into account. *Id.* (citations omitted).
[77] *Ortho-McNeil Pharm., Inc.*, 348 F. Supp. 2d at 749.
[78] *Id.* (emphasis added); *see also In re* Chupp, 816 F.2d 643, 647 (Fed. Cir. 1987) ("Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a prima facie case of obviousness.").
[79] Darrow, *supra* note 22, ¶ 47.
[80] *In re* Chupp, 816 F.2d at 644 (finding a "claimed compound gave superior results . . . [that were] at least five times greater than those of the closest prior art compounds" was patentable); *see also* United States v. Ciba-Geigy Corp., 508 F. Supp. 1157, 1169 (D.N.J. 1979) (finding a tenfold increase in activity was patentable over a similar patented compound); *In re* Wiechert, 370 F.2d 927, 932 (C.C.P.A. 1967) (finding a sevenfold increase in activity was patentable over a closely related compound).

efficacy compared to the predicted efficacy.[81] Further, the court in *Ortho-McNeil* reasoned that an improvement in one favorable property often comes at the expense of another favorable property. Therefore, when an enantiomer improves over the prior art racemate in several areas, this weighs toward an unexpected result that leads to patentability.[82]

ii. Secondary Considerations

Secondary considerations "alone may defeat a claim of obviousness."[83] Those considerations include whether the patented invention had commercial success,[84] was copied by competitors,[85] was licensed,[86] answered a long felt need,[87] was successful despite the failure of others,[88] was praised by peers,[89] or was met by skepticism from others in the industry.[90] The patent challenger then has the burden to rebut these considerations. As Darrow points out, commercial need and copying by competitors will almost always favor the patent holder.[91] In establishing commercial success, the patent holder need only show "significant sales in a relevant market . . . ."[92] Additionally, the patent challenger normally would not contest the patent unless the challenger wanted to copy the patent.[93] These two factors both weigh in favor of a non-

[81] *In re* Carabateas, 357 F.2d 998, 1001 (C.C.P.A. 1966) (Rich, J., concurring) ("The question is not . . . 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.").
[82] *Ortho-McNeil Pharm. Inc.*, 348 F. Supp. 2d at 749 (finding that a compound that "is twice as potent, about ten times more soluble, and appreciably less toxic" is unexpected). In O*rtho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, the court determined that improvement of one property often comes at the expense of another. Therefore, this improvement in several areas was unexpected. *Id.*
[83] *Id.*
[84] *In re* Piasecki, 745 F.2d 1468, 1473 (Fed. Cir. 1984).
[85] Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380-82 (Fed. Cir. 1986).
[86] Darrow, *supra* note 22, ¶ 52.
[87] *Id.*
[88] Sterling Drug Inc. v. Watson, 135 F. Supp. 173, 173 (D.D.C. 1955).
[89] Brenner v. Ladd, 247 F. Supp. 51, 53-54 (D.D.C. 1965).
[90] Darrow, *supra* note 22, ¶ 52.
[91] *Id.* ¶ 53.
[92] Alza Corp. v. Mylan Labs. Inc., 388 F. Supp. 2d 717, 740 (N.D. W. Va. 2005).
[93] Pfizer Inc. v. Ranbaxy Labs. Ltd., 405 F. Supp. 2d 495, 518 (D. Del. 2005).

obviousness patent.[94]

iii. A Non-obvious or Unknown Resolution Method

Finally, even if prima facie obviousness is established and neither improvements nor secondary considerations can successfully rebut the finding, the enantiomer can still be shown to be non-obvious if the patent holder used a non-obvious separation technique to resolve the enantiomers.[95] Because enantiomers have equivalent chemical and physical properties, the separation of these molecules can be exceedingly difficult. For this reason, resolution of the enantiomers has been used to rebut prima facie obviousness. It has also been the case that isolation of a single enantiomer from the racemate does not render the isolation of the other enantiomer obvious.[96]

IV. PROPOSED SCHEME FOR PREVENTION OF PRODUCT HOPPING

The next task is to determine adjustments that could be made to the current patent doctrine to better prevent product hopping for enantiomer patents. This proposed adjusted doctrine specifically applies only to previously patented racemates and the later patenting of their individual enantiomers. This new system is applied below to two similar, but distinguishable enantiomer patenting cases. One case has been labeled product hopping and the other has not. If this analysis better targets the product hopping patent then it could be useful in court determinations of patentability and patent validity.[97] The first case study that this Note examines is the Prilosec to Nexium (omeprazole to (-)-omeprazole) product hop. Then, the Floxin to

[94] *Id.*
[95] *In re* Hoeksema, 399 F.2d 269, 274 (C.C.P.A. 1968) ("[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds." (citation omitted)).
[96] Brenner v. Ladd, 247 F. Supp. 51, 55 (D.D.C. 1965) (finding that the prior art method used for isolating the patented compound predicted the precipitation of the opposite enantiomer over the claimed enantiomer, and was therefore nonobvious).
[97] This would also be useful in determining patentability.

Levoquin (ofloxacin to levofloxacin) patenting is examined. To perform this analysis, we will use the issued formulation patents of these compounds for reference. After each new standard is introduced, that standard is applied to the case studies.

a. The New Standard for Establishing Prima Facie Obviousness

i. POSITA Defined

The court's analysis would proceed as follows in establishing what a POSITA is in regard to the pharmaceutical industry. A person of ordinary skill in the art in the pharmaceutical industry is typically a chemist. A chemist understands that quaternary carbons, sulfoxides substituted with different groups, and other stereogenic centers give rise to enantiomeric mixtures during syntheses.[98] A chemist also understands that enantiomers can have different biological properties from either the racemate or other individual stereoisomer.[99] Therefore, the POSITA understands the value of separating an enantiomer from its racemate.

ii. Motivation

The knowledge that the POSITA has will always provide the *motivation* to attempt to separate an enantiomer in the proposed doctrine. Though the court warns against the use of generalizations in finding motivation, racemates could be an exception to this rule for at least three reasons. First, motivation is rebuttable, so this can be overcome by defendants with compelling evidence. Second, enantiomer patenting is an area that is uniquely susceptible to product hopping, so the court should hold these patents to a higher standard. Third, there are many known separation techniques, so the incentive to separate enantiomers will always be high, at least in attempting to separate the enantiomers.

[98] This knowledge has been available as early as 1946, and has been used in the courts analysis since 1960. *See, e.g.*, *In re* Adamson, 275 F.2d 952, 954 (C.C.P.A. 1960).
[99] This type of analysis was used in 1960 by courts, thus the relevant time frame allows us to make this assessment. *See id.*

Also, because the POSITA has at her disposal many references demonstrating improved properties of racemates, there is at least a "reasonable expectation" that separation of the current racemate will also produce such an outcome. Accordingly, a reasonable expectation of success is established at the outset for a given racemate.

iii. Structural Similarities with Prior Art Compounds and Genus Size

Structural similarity standards, as articulated above, weigh heavily toward an obviousness finding for racemates. Enantiomers differ only in their three dimensional shape, but are otherwise structurally equivalent and enantiomers belong to a genus of exactly two. The standards that the courts have articulated are consistent with the current analysis and would help limit product hopping in racemates. Therefore, these standards will remain unchanged.

iv. Prima Facie Obviousness Summary Under the New Standard

As articulated above, the prima facie case has been established solely based on the product being an enantiomer separated from a previously disclosed racemate. In the current analysis, courts would accept an enantiomer as prima facie obvious in light of a previously patented racemate containing that enantiomer. The desire to improve pharmaceutical activity and lower side effects along with the availability of many separation techniques provides motivation to isolate an enantiomer. This motivation is bolstered by an expectation of success because many enantiomers are patented with improved properties over their parent racemates.

A. Applying the Proposed Standard Prima Facie Obviousness Standard

We now apply these new standards our case study of (-)-omeprazole and levofloxacin. Because both (-)-omeprazole and levofloxacin involve patenting enantiomers derived from previously disclosed racemates, prima facie obviousness is established. Because prima facie

obviousness is established, the *Graham* factor analysis need not be performed.[100] This means in the case of enantiomer patenting after the patenting of a racemate, there is a presumption of obviousness that must be rebutted. The following section outlines the standards for rebutting this prima facie obviousness finding.

b. Rebutting Prima Facie Obviousness Under the New Standard

i. Unexpected Improvement in Results

What constitutes an unexpected result is the single most important area in which better guidance and higher standards may better discourage product hopping for enantiomers. As such, it is given more weight than either secondary factors or novel separation methods in a court's analysis.[101] A finding that there is an "unexpected improvement in results" is dispositive for non-obviousness in this analysis.

In looking for unexpectedly improved results, the analysis investigates intrinsic information from the issued enantiomer patent. Furthermore, only *pharmaceutically relevant* properties will be used when investigating a new pharmaceutical.[102] Therefore, overall efficacy, quantifiable side-effects, and toxicity of the enantiomer are weighted the heaviest in this determination. In studies purporting to show "unexpected results," direct causal relationships must be established.[103] Moreover, all of these results must be supported with clinical data as well as qualitative data where relevant. Finally, factors such as solubility will only be weighed to the

[100] It should be noted that if an enantiomer is synthesized through asymmetric synthesis, this analysis would not be in effect. When a compound is synthesized asymmetrically, the Court's current analysis would be performed and these compounds would be looked at ad hoc.
[101] Only rarely will secondary factors overcome a finding of "expected results." Additionally, for a novel separation method to overcome "expected results" that separation must be absent in prior art.
[102] The term "pharmaceutically relevant" means properties concerning efficacy of the drug and other properties that would actually lead to more or less prescribing of a drug. For example, lower frequency or minor side-effects are less relevant and higher frequency or major side-effects are more relevant.
[103] For example, in demonstrating lower side-effects, the relevant measure would be the incidence of side-effects or at least a measure of the incidence of release of an agent that induces that side effect directly. A measurement of an agent that has been correlated to increased incidence of a side effect is not a direct correlation. This increased incidence of release of an agent could be another side effect and not the cause of the side effect in question.

extent that they deliver a true clinical advantage.

A. Setting a Baseline for Expected Results

The unexpected result determination hinges on how we define the properties of the racemate, the purified enantiomer, the removed enantiomer, and the relationship between the three.[104] Where the baseline reference point is set, with respect to improvement of properties of the purified enantiomer, will determine just what constitutes an "unexpected" result. In this analysis, the purified enantiomer's properties will range from it having all of the properties (good or bad) of the racemate, to sharing the same properties with the removed enantiomer. In other words, the removed enantiomer then has expected properties ranging from being completely benign, acting only as an equal weight-equivalent of a space-filler,[105] to having completely identical properties to the active ingredient.[106]

From this baseline understanding, assessments about what is within the expected range of results are made. We will define two cases—"A" and "B"—as the extreme perimeters encompassing the expected range. Properties outside this range will then be unexpected. At one end of the spectrum, in case A, the purified enantiomer is separated from a completely benign enantiomer. In this case, we would expect to see an activity improvement of two for active enantiomer compared to an equal weight of racemate. This result is a linear relationship between the activity and dose amount, in the presence of or removed from the racemic mixture.[107] For this extreme, one would also expect the side effects to become more severe and the toxicity to

[104] For simplicity, the removed enantiomer will be referred to as the "inactive" enantiomer.
[105] This is consistent with the reasoning in the *Ortho-McNeil Pharmaceutical, Inc.* case. Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 348 F. Supp. 2d 713, 749 (N.D. W. Va. 2004) (where the court took testimony that one enantiomer was an "impure" substance compared to the active ingredient).
[106] This covers a range of the removed enantiomers activity. If the enantiomer had equivalent efficacy, the separation of the two yields no improvement in results. If the benign enantiomer has no efficacy, this is also to be expected and its removal again gains little.
[107] This presumption of course depends on the activity profile of the drug, but if we expect linearity in the therapeutic range, then these assumptions can be made.

increase by a factor of two.[108] At the other end of the spectrum, in case B, if the removed enantiomer were exactly *as effective* as the purified enantiomer, then the racemate activity per unit of weight would be equivalent to the purified racemate's activity per unit of weight.[109]

Those two extremes define the border around what is expected; if the properties stray from between these baseline expectations, this works toward a finding of "unexpected results." For instance, an improvement of efficacy by a factor of two or less would be an expected result in this analysis. At the same time, an improvement by a factor of two, with a corresponding decrease in side-effects would be unexpected—because the relevant expected range would be a two-fold increase in incidences of side-effects in case A, or equivalent side-effects in case B.

These findings could then be rebutted by a showing that these properties were predicted in the prior art. If no showing can be made, then the enantiomer is non-obvious and the analysis can stop. The challenger has not carried its burden. This analysis is consistent with preventing the patenting of only product hopping compounds, while allowing patenting of legitimately improved compounds.

B. Unexpected Improved Results Case Study: Omeprazole to Esomeprazole

Patent 5,877,192 is for the use of (-)-omeprazole in the "treatment of gastric acid related diseases by inhibition of gastric acid secretion . . . ."[110] The patent discloses that "omeprazole exhibits polymorphic metabolism, i.e. a few individuals (3% among the Caucasian populations and 15-20% of [East Asians]) 'metabolise' omeprazole slowly (slow metabolisers) compared to

[108] This is again because the same dose will now have twice the potency, assuming the active API has all of the properties.
[109] As would all of the other properties.
[110] U.S. Patent No. 5,877,192 (filed Apr. 11, 1997) (also disclosing that "[m]ore than 135 million prescriptions by doctors indicate that omeprazole is an effective and safe drug").

the rest of the population (rapid metabolisers)."[111]

The claimed purified enantiomer of omeprazole, (-)-omeprazole[112] was found to have "less interindividual variation . . . [in] especially slow versus rapid metabolisers, and on the average higher plasma levels giving higher dose efficiency in patients, [which] could be of therapeutic benefit."[113] The patenting of this invention was therefore based on "higher dose efficiency and less interindividual variation."[114] These will be addressed in turn and then together as to whether they constitute a non-obvious "unexpected results" under the new standard.

1. Higher Dose Efficiency

Does having the (-)-omeprazole compound free of the racemate improve the effect of the (-)-omeprazole in an unexpected way?[115] The patent holder states:

> It was observed that the steady-state [area under the curve] of (-)-omeprazole in an average population was significantly higher (2-fold) than that of omeprazole racemate when each compound was given repeatedly in 20 mg daily doses. Therefore, the anti-secretory effect, which is directly correlated to the [area under the curve] irrespective of compound, was higher for (-)-omeprazole than for omeprazole racemate following administration of identical doses.[116]

The patent holder goes on to write that this result should give higher healing rates in a shorter timeframe and that "[i]t might also be expected that a more rapid symptom relief will be obtained."[117]

Under the proposed analysis, this two-fold increase alone would not be enough to constitute an unexpected result. Additionally, speculation on this being "expected" to give better

[111] *Id*.
[112] The active ingredient in Nexium.
[113] '192 Patent.
[114] *Id*.
[115] It is important to note that the patentee in this case did not make the most relevant comparison. Comparisons between equal weights of the (-)-omeprazole and omeprazole were made. This means that pure compound had twice the dosage of the (-)-omeprazole. A better comparison would have been between the (-)-omeprazole and twice the weight equivalent of the omeprazole racemate.
[116] '192 Patent.
[117] *Id.*

results does not add to the analysis unless there is clinical data supporting it.[118]We now turn to the question of the importance of interindividual variation.

2. Interindividual Variation

From the study, the patent holder found that the mean drug plasma concentration between slow and rapid metabolisers varied more when omeprazole was administered than when (-)-omeprazole was administered. The patent holder indicates that "after correction for different dose levels, the resulting difference in [omeprazole in the area under the curve] between slow and rapid metabolisers was almost 10-fold for omeprazole and only 3-fold for the (-)-enantiomer of omeprazole."[119]

Several things can be noted about the studies performed by the patent holder initially. First, four times higher dosing was given to the slow metabolisers than the rapid metabolisers.[120] Second, the slow metabolisers were given doses outside the range of typically prescribed therapeutic levels. Third, the studies were done with only five test subjects for the slow metabolisers and four test subjects for the rapid metabolisers. Fourth, neither the standard deviation nor the statistical significance of these numbers was indicated. Fifth, and most importantly, the measurement accounted for the amount of (+) and (-)-omeprazole in the blood, and did not disclose the amount of "gastrin" in the patient.

As stated previously, in determining "unexpected results" concerning side effects, studies need to make relevant comparisons and these results must be supported with clinical data. Barring discussions pertaining to whether these results are statistically significant, there remains

[118] *See* Yoseph Caraco et al., *Ethnic and Genetic Determinants of Omeprazole Disposition and Effect*, 60 CLINICAL PHARMACOLOGY & THERAPEUTICS 157, 166 (1996) ("The need for dosage adjustment in subjects with diminished CYP2C19 activity and in Chinese deserves further evaluation.").
[119] '192 Patent.
[120] *Id.* (this was to "measure the potential effect on caffeine metabolism in slow metabolisers" which did not enter into this study).

the question of whether the resulting rise in (+) and (-)-omeprazole in the blood is pharmaceutically relevant.

The pharmaceutically relevant comparison should not be whether the level of (±)-omeprazole in the blood is higher, but whether the patients receiving racemic omeprazole are more likely to develop hypergastrinemia. The development of hypergastrinemia is directly correlated to the amount of gastin produced in the patient.[121] The patent holder claims that: "Since the gastrin levels obtained simply are a result of a natural feedback mechanism determined by the degree of inhibition of gastric acid secretion, the use of the (-)-enantiomer of omeprazole may also potentially result in a less pronounced increase in gastrin in slow metabolisers." This may be in direct conflict with their prior higher dose efficiency data which shows the gastric acid secretion is better suppressed by equal dosing of (-)-omeprazole.[122]

In this context the data actually suggests that (-)-omeprazole has the expected effect of increasing gastrin secretion, and therefore hypergastrinemia.[123] The data gives the "expected" result that increased efficacy yielded increased side-effects.[124] This result, combined with the predictable two-fold increase in activity, would not lead to a finding that (-)-omeprazole has unexpectedly improved properties. Instead, this result weighs heavily toward an obviousness finding under the proposed standard.

C. Unexpected Improved Results Case Study: Ofloxacin to (-)-Ofloxacin

Ofloxacin is an anti-microbial agent having an asymmetric carbon atom at the "3-

[121] *See* Derek Gillen et al., *Esomeprazole 40mg Twice Per Day Causes More Marked Rebound Acid Hypersecretion Than Omeprazole 40mg Per Day*, 124 GASTROENTEROLOGY A-233 (2003).
[122] Gastrin levels have since been shown to actually be higher for Nexium than Prilosec. *See Id.*
[123] *Id*.
[124] This at least does not dispute it that these side effects would increase.

position" that gives rise to a racemic mixture.[125] The (-)-ofloxacin enantiomer, the API in Levaquin,[126] was found to have two-fold higher antimicrobial activity than the ofloxacin racemate (Figure 2).[127] The acute toxicity of the antimicrobial (LD_{50}) was 203 mg/kg for ofloxacin and 244 mg/kg for (-)-ofloxacin. This data shows that the toxicity actually decreases, while the effectiveness increases by a factor of two. Though increased efficacy would not by itself lead to unexpectedly improved results, when coupled with lower toxicity both these factors show non-obviousness.

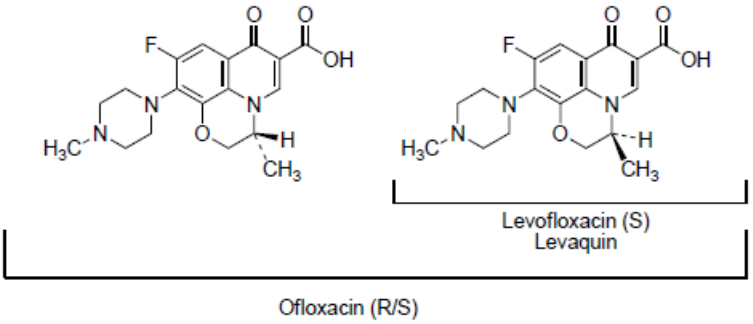

Figure 2. The mixture of the (+) and (-)-enantiomers yield ofloxacin. The (-)-enantiomer alone gives levofloxacin, the API of Levaquin®.

Finally, the solubility data shows that (-)-ofloxacin was over ten times as soluble as ofloxacin. This finding is pharmaceutically relevant because it lends support to use of this enantiomer in intravenous administration.[128] By unexpected results alone, ofloxacin would overcome obviousness. The analysis for (-)-ofloxacin can therefore stop here with a finding of

[125] U.S. Patent No. 5,053,407 (filed June 20, 1986).
[126] This is a product of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
[127] '407 Patent (note that the (+)-ofloxacin enantiomer had activity ranging from 1/10 to 1/100 of the racemate, depending on the microbe used in the study).
[128] U.S. Patent No. 5,053,407 (filed June 20, 1986).

non-obviousness.

ii. The New Standard for Secondary Considerations

As discussed previously, some secondary considerations will almost always weigh in favor of the patent holder. These include copying by others and commercial success. In the case of racemates, copying will be removed from the analysis altogether. For racemates, "copying" an enantiomer may not in fact be copying. The genus of possible compounds is only two and the structural similarity between the racemate and enantiomer is as similar as it possibly could be.[129] Therefore, it would be very difficult to assess whether synthesizing the enantiomer was copying or just the obvious next choice for all researchers in that pharmaceutical area.[130]

Additionally, commercial success is difficult to evaluate for racemates to enantiomers. For an FDA approved racemic mixture that has commercial success, the commercial success of the following enantiomer may be due in part to the success of the racemic mixture and campaigning by the company for the new product. Factual inquiries can be made on this matter, but in the new doctrine, the court will give this consideration little weight in its analysis.

The considerations left in the new analysis include whether the patented invention was licensed, answered a long felt need, was successful despite the failure of others, was praised by peers, or was met by skepticism from others in the industry. Whether the invention had commercial success receives less emphasis. It is important to note that the answers to these inquiries change with time.

A. Secondary Considerations Case Study: Omeprazole to (-)-Omeprazole

[129] In fact, 50% of the racemic mixture is equivalent to the purified enantiomer.
[130] This analysis would of course change for other pharmaceutical compounds that are not enantiomers from previously disclosed racemates. In cases not involving racemates, the obviousness of the "copied" compound would lend more toward a finding of copying because there may be more structural variation compound to compound, and the genus will likely be much larger.

We perform this analysis as though the patent were being challenged today. Because litigation surrounding the validity of the (-)-omeprazole patent is pending and no discovery has been performed, information and analysis of these considerations cannot be fully fleshed out. That being the case, any information pertaining to secondary factors available can be used in this analysis.

First, has (-)-omeprazole been licensed? Relevant to this inquiry is the patent validity challenge by Ranbaxy Pharmaceuticals Inc.[131] to the (-)-omeprazole patent. This litigation was settled, and Ranbaxy was granted an exclusive license to (-)-omeprazole for 180 days at the end of the patent life.[132] Other licensing deals could not be found, but at least two other challenges to the patent were found.[133] Choosing to challenge the patent, rather than license it, points toward patent invalidity, weighing against patent validity.

Second, did this drug answer a long felt need? The short answer is no. Omeprazole was used for the treatment of the exact same condition as (±)-omeprazole. Further, (±)-omeprazole successfully treated patients' symptoms prior to the release of (-)-omeprazole.

Third, was the patent holder successful despite the failure of others? This question can be viewed as an inquiry into the efficacy of the drug and resolution of (-)-omeprazole.[134] As stated previously, because (±)-omeprazole is successful in treating GERD, this factor weighs in favor of the (-)-omeprazole patent challenger. Additionally, from the (-)-omeprazole patent, the separation of the enantiomers had been performed on both analytical scale and in preparative scale years

[131] This is a generic drug provider.
[132] *Ranbaxy and AstraZeneca Reach Agreement in Esomeprazole Patent* Litigation, BIO-MEDICINE, Apr. 15, 2008, http://www.bio-medicine.org/biology-technology-1/Ranbaxy-and-AstraZeneca-Reach-Agreement-in-Esomeprazole-Patent-Litigation-4608-1/.
[133] *See* Astrazeneca AB v. Ranbaxy Pharms., Inc., No. 05-5553, 2008 WL 5272018, at *1 (D.N.J. Dec. 16, 2008); *see also* Dr. Reddy's Labs., Ltd. v. AstraZeneca AB, No. 08-2496, 2008 WL 4056533, at *1 (D.N.J. Aug. 28, 2008).
[134] *See* discussion *infra* Part IV.b.iii.A (addressing success in separation).

before the disclosed separation.[135] This weighs against a finding that others failed in the separation of the single enantiomer from the mixture.

The last pertinent secondary consideration is whether the invention had commercial success. This consideration can be rebutted with data showing that marketing of the drug accounted for the success. In the case of (-)-omeprazole, AstraZeneca spent large amounts on marketing it and dropped all marketing of the predecessor omeprazole.[136] Given the little gain in clinical efficacy, this weighs toward commercial success being attributable to marketing rather than based on the drug itself.

With these factors in mind, secondary factors do not weigh toward patent validity for (-)-omeprazole. The last inquiry is therefore whether the separation was non-obvious or novel.

iii. Non-obvious Separation

Using the new standard, if there is a literature reference describing a previous separation of the enantiomer in question, then a non-obvious separation cannot be claimed by the patent holder. This standard will aid the court in disincentivizing an inventor from deliberately avoiding disclosed separation methods in attempts to show non-obviousness. Other than this, the POSITA is faced with many known racemate resolution techniques and, for that reason, these techniques become "obvious-to-try" as noted by *KSR*.

A. Novel Separation Case Study: Omeprazole to (-)-Omeprazole

As stated previously, the (-)-omeprazole patent discloses the prior successful

[135] U.S. Patent No. 6,875,872 (filed Oct. 16, 2000).
[136] Harris, *supra* note 11 ("The company is pouring huge money into this. It spent $478 million promoting Nexium in the U.S. last year, according to research firm IMS Health. Nexium is currently the most heavily advertised drug in the U.S."); *see also* Gladwell, *supra* note 29 ("To keep cheaper generics at bay, and persuade patients and doctors to think of Nexium as state of the art, AstraZeneca spent half a billion dollars in marketing and advertising in the year following the launch. It is now one of the half-dozen top-selling drugs in America.").

separation of the (-)-omeprazole from (±)-omeprazole at the analytical scale and preparative scale.[137] This finding is dispositive for an obvious separation, because the disclosed claimed technique could have been later developed solely to produce rebuttal evidence.

c. Final Analysis

For the omeprazole hop, (-)-omeprazole failed a validity analysis based on obviousness under all three rebuttal phases. On the other hand, the ofloxacin to (-)-ofloxacin patent was found to be valid and a non-obvious improvement over the racemate. These are, of course, just two examples of enantiomer patents, but the preliminary analysis shows that this standard could be workable. More case studies should be performed to further develop the test.

Incentives in the case of pharmaceuticals must be kept high to protect inventions that are particularly susceptible to infringement from being copied. Finding product hopping drugs is a difficult task in itself, and labeling true innovations as product hops creates the risk of preventing inventions in the area of enantiomers. Concentrating on whether a later disclosed enantiomer has "unexpected improved results" may enable targeting of obvious inventions more effectively.

V. CONCLUSIONS

By establishing the prima facie case and adjusting the rebuttal standards for enantiomers, product hopping can more effectively be targeted. The key to the proposed analysis is better description of the standards for "unexpected improved results." In the product hopping case for Prilosec to Nexium, this new doctrine seems to work. However, special care must be taken in making case-to-case generalizations. Because pharmaceutical companies are uniquely susceptible to infringers, more case studies should be performed before adopting any modified doctrine.

[137] U.S. Patent No. 6,875,872 (filed Oct. 16, 2000).