DEUTERATED DRUGS: UNEXPECTEDLY NONOBVIOUS?

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I. Introduction

The pharmaceutical industry depends heavily on the market exclusivity afforded by patent protection to recoup research and development costs associated with FDA-approval of new drugs.[1] Of particular importance to the validity of pharmaceutical patents is the obviousness requirement codified in 35 U.S.C. § 103.[2] Although nonobviousness is a requirement of

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[1] Michael Enzo Furrow, *Pharmaceutical Patent-Life Cycle Management After* KSR v. Teleflex, 63 FOOD & DRUG L.J. 275, 278 (2008). Development and regulatory approval of a clinical candidate typically exhausts half of the patent term, substantially decreasing the market exclusivity for the inventor and the income derived thereof. *Id.* On average, the development time for an approved drug ranges from ten to fifteen years, at a total cost of $1.5 billion per approved drug. *Id.* at 283.

[2] "A patent may not be obtained though the invention is not identically disclosed . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (2006). *See also* Andrew V. Trask, Note, *"Obvious to Try": A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 FORDHAM L. REV. 2625, 2640 (2008) (arguing that nonobviousness has been termed "the ultimate condition of patentability"); Gregory Mandel, *The Non-Obvious Problem: How the Indeterminate Nonobviousness Standard Produces Excessive Patent Grants*, 42 U.C. DAVIS L. REV. 57, 63 (2008) (stating that the importance of the nonobviousness requirement is demonstrated by the fact that it is the most

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all issued patents, pharmaceutical patents are especially susceptible to an obviousness challenge because the natural progression of science necessarily builds upon past discoveries and requires considerable experimentation through trial and error, thereby potentially rendering the invention obvious-to-try.[3] The Federal Circuit (and its predecessor, the Court of Customs and Patent Appeals, or "CCPA") has therefore tailored the obviousness requirement to the unique challenges inherent in the chemical arts by outlining ways in which an applicant may overcome an obviousness challenge.[4]

The pharmaceutical industry utilizes patent law to protect a variety of discoveries, including: compositions of matter,[5] manufacturing processes,[6] new uses or formulations of previously protected compositions of matter,[7] and biological

commonly litigated validity issue and the requirement most likely to result in patent invalidation).

[3] *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, 477 (2008).

[4] *See, e.g., In re* Papesch, 315 F.2d 381, 386 (C.C.P.A. 1963) (holding that structural similarity between the prior art and the claimed compound supports a prima facie case of obviousness, which is rebuttable by evidence that the claimed compound exhibits unexpected or surprising properties that the prior art does not possess). The *Papesch* court further explained that a chemical compound and its properties are inseparable because the formula drawn in a patent merely identifies the compound being patented and is not the invention. *Id.* at 391.

[5] Chemical compositions of matter are the primary focus of this Note.

[6] *See* Furrow, *supra* note 1, at 297. Patenting the method of making pharmaceutical agents is an important defensive strategy because generic companies are prevented from utilizing the patented synthetic route and must either design a novel synthesis of the compound, which can be costly, or wait for the method patent to expire. *Id.*

[7] *See, e.g.,* Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc., 429 F.3d 1364 (Fed. Cir. 2005) (discussing a new formulation of a drug which minimized undesirable properties); Merck & Co. v. Teva Pharmaceuticals USA, Inc., 395 F.3d 1364 (Fed. Cir. 2005) (discussing an optimized dosing regime which sought to improve patient compliance); Bayer Schering Pharma AG v. Barr Laboratories, Inc., No. 05-cv-2308, 2008 WL 628592 (D.N.J. Mar. 3, 2008), *aff'd*, 575 F.3d 1341 (Fed. Cir. 2009) (discussing the improved formulation of a drug by micronization); Alza Corp. v. Mylan Laboratories, Inc., 388 F. Supp. 2d 717 (N.D.W. Va. 2005) (discussing controlled-release formulation); Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348 (Fed. Cir. 2007) (discussing an improved acid addition salt of a patented drug); Aaron Smith, *Merck pitches another use for*

mechanisms of action.[8] Patents on chemical compositions of matter, new salt forms, and new formulations are the most vulnerable to obviousness challenges because the subject matter may be substantially similar to the prior art.[9] Structural similarity between the prior art and a claimed compound is not usually a chance occurrence.[10] As such, pharmaceutical applicants and patentees must be prepared to offer evidence of nonobviousness, either contained in or ancillary to the application.[11]

Gardasil, CNNMONEY, Dec. 16, 2005, http://www.CNNMoney.com, *archived at* www.webcitation.org/5bad4sRWL (discussing that Gardasil®, in addition to preventing the sexually transmitted human papilloma virus (HPV), is also highly effective in preventing the sexually transmitted viruses that cause vaginal lesions and genital warts in women).

[8] *See* Furrow, *supra* note 1, at 298 (stating that inventors attempt to patent all possible medical uses of a drug when preliminary assays identify the biological pathway on which the drug acts).

[9] Patents on new salt forms or new formulations are most often obtained by the owner of the patent for the composition of matter. *See, e.g., Pfizer v. Apotex*, 480 F.3d at 1354.

[10] *See* RICHARD B. SILVERMAN, THE ORGANIC CHEMISTRY OF DRUG DESIGN AND DRUG ACTION 2 (2d ed. 2004). As of 2004, many of the drugs on the market were derived from natural products, including sixty percent of the anti-cancer and anti-infective agents. *Id*. Drugs currently on the market can serve as lead compounds for second generation compounds, as demonstrated in the case of tranquilizers Librium® and Valium®. *Id.* at 11. Further, metabolites identified during clinical trials may exhibit desirable side effects which can be exploited to yield another active drug—the nonsedating antihistamine terfenadine was shown to be metabolized to another nonsedating antihistamine, fexofenadine, having a better safety profile and now marketed as Allegra®. *Id.* at 14. A side effect observed during clinical trials may also lead to alternative indications of a drug—Dramamine® was originally designed as an antihistamine but was more effective against motion sickness, and Viagra® was originally designed for the treatment of angina and hypertension but was found to be more effective for treating erectile dysfunction. *Id.* at 15.

[11] Harris A. Pitlick, *Some Thoughts About Unexpected Results Jurisprudence*, 86 J. PAT. & TRADEMARK OFF. SOC'Y 169, 169 (2004) (arguing that evidence of unexpected results is the most prevalent form of evidence of nonobviousness).

II. Pharmaceutical Arts Background

A. Drug Metabolism

A pharmaceutical drug participates in two general categories of interactions within the body. The pharmaco-dynamic effect of a drug describes the interaction between the drug and its biological target, most often a receptor.[12] This interaction occurs through the drug's pharmacophore or groups on the molecule which directly interact with the target receptor.[13] In addition to the effect of the drug on its biological receptor, the drug is also susceptible to biological processes, called pharmacokinetics, which are designed to eliminate the foreign agent from the body.[14] Rational approaches to drug design target these processes within the body to improve drug-receptor interaction (pharmacodynamics) and achieve an improved metabolic profile (pharmacokinetics).[15] Because a strong interaction between the drug and its receptor is meaningless if the drug is metabolized so rapidly that it never reaches its target, many drug discovery programs seek to attenuate the pharmacokinetic properties of a drug candidate early in the development process.[16]

Drug metabolism causes pharmacological deactivation of a drug by modifying its structure so that it is no longer capable of interacting with its biological receptor and is more readily excreted from the body.[17] Metabolism of a drug often generates products which have different biological activities and may be

[12] *See* SILVERMAN, *supra* note 10, at 17-18.

[13] *See* SILVERMAN, *supra* note 10, at 17-18 (stating that only a small part of a drug may be involved in receptor interaction and the other atoms may serve to maintain the overall conformation of the pharmacophore or may be leveraged to improve the physical properties of the drug).

[14] *See* SILVERMAN, *supra* note 10, at 18. Pharmacokinetics is a general term for the absorption, distribution, metabolism, and excretion (ADME) of a drug within the body. Although all of these processes contribute to a drug's effectiveness, this Note is primarily concerned with the metabolism of a drug within the body.

[15] *See* SILVERMAN, *supra* note 10, at 51.

[16] *See* SILVERMAN, *supra* note 10, at 51 (stating that pharmacokinetic problems are responsible for the failure of about 40% of drugs in clinical trials).

[17] *See* SILVERMAN, *supra* note 10, at 415.

responsible for toxic or carcinogenic side effects.[18] Additionally, rapid metabolism decreases the drug's half-life and concentration in the bloodstream, thereby reducing its efficacy.[19] Because metabolism studies are essential to the evaluation of drug safety and efficacy, the FDA requires an understanding of the metabolic pathways in both humans and animals prior to regulatory approval.[20] As our understanding of metabolic processes improves, pharmaceutical companies increasingly exploit metabolites in an effort to control the down-stream effects of their drugs through a technique called metabolism-induced drug design.[21]

B. Deuterium and Kinetic Isotope Effects

Isotopes are atoms which have nearly identical properties but which have different masses due to changes in the number of neutrons in their nuclei.[22] One of the most widely used isotopes in the pharmaceutical industry is deuterium, an isotope of hydrogen with a nucleus comprising one neutron and one

[18] *See* Allan B. Foster, *Deuterium Isotope Effects in the Metabolism of Drugs and Xenobiotics: Implications for Drug Design*, 14 ADVANCES IN DRUG RESEARCH 1, 2 (1985); SILVERMAN, *supra* note 10, at 406.

[19] *See* Foster, *supra* note 18, at 2. Efficacy is defined as the ability of the drug to initiate a biological response. SILVERMAN, *supra* note 10, at 138.

[20] *See* SILVERMAN, *supra* note 10, at 407.

[21] *See* Foster, *supra* note 18, at 2. Traditional structure modifications made to reduce metabolism usually include blocking the metabolically labile site with larger functional groups or with groups that are not prone to metabolism, altering the solubility of the molecule, or changing the electronics of the surrounding functional groups such that the metabolically labile group is no longer a suitable substrate for the enzyme. Foster, *supra* note 18, at 5. Alternatively, it is possible to design a compound that is inactive when administered, but which is metabolized to its active form in vivo. SILVERMAN, *supra* note 10, at 408.

[22] DAVID W. OXTOBY & NORMAN H. NACHTRIEB, PRINCIPLES OF MODERN CHEMISTRY 19 (3d ed. 1996). Atoms are comprised of a nucleus surrounded by an electron cloud. *Id.* at 18. The nucleus contains both protons, which carry a positive charge (+1), and neutrons, which are neutral particles. *Id.* In a neutral atom, the number of protons equals the number of electrons (which carry a negative charge, –1), and the overall charge of an atom results from an imbalance of protons and electrons. *Id.* Because neutrons are neutral particles, they do not contribute to the electrostatic charge of an atom, and therefore do not contribute to the atom's chemical reactivity.

proton.[23] Because deuterium and hydrogen exhibit nearly identical physical properties, deuterium substitution is the smallest structural change that can be made on a molecule.[24] Thus, a parent compound and its deuterated counterpart have nearly identical physiochemical properties.[25] The substantial similarity between a deuterated and parent compound, also called the protio version, is exploited in drug discovery programs through isotopic labeling techniques[26] to identify and quantify metabolites in an effort to understand metabolism-mediated toxicities.[27]

Kinetic isotope effects are the observed changes in the rate of reaction that occur when deuterium is substituted for hydrogen.[28] Deuterium isotope effects result from the greater

[23] *Id*. at 19. The hydrogen atom is comprised of one proton in its nucleus and one electron. *Id.* The deuterium nucleus, in contrast, has a neutron and a proton, and thus weighs more than hydrogen. *Id*. The atomic masses for deuterium and hydrogen in atomic mass units (amu) are 2.014 amu and 1.0078 amu, respectively. Robert L. Wolen, *The Application of Stable Isotopes to Studies of Drug Bioavailability and Bioequivalence*, 26 JOURNAL OF CLINICAL PHARMACOLOGY 419, 420 (1986).

[24] *See* Foster, *supra* note 18, at 5 (deuterium substitution has a negligible effect on sterics and physiochemical properties).

[25] *See* Thomas A. Baillie, *The Use of Stable Isotopes in Pharmacological Research*, 33 PHARMACOLOGICAL REVIEWS 81, 85 (1981) (stating that the isotope-labeled species and its unlabeled counterpart have nearly identical physiochemical properties such that the only way to distinguish them is by their different masses).

[26] *See* Foster, *supra* note 18, at 3. Isotopic labeling is a technique whereby an isotope, usually deuterium, is selectively incorporated into a clinical candidate. *See* Foster, *supra* note 18, at 5. The deuterated version is co-administered with the parent species, and the resulting metabolites are separated according to their different masses by mass spectrometry. Baillie, *supra* note 25, at 85. Because the mass of the deuterated species is increased by one amu for every deuterium atom on the molecule, it is possible to identify metabolites in the presence of other biological entities by the dual signals for the parent and deuterated species. *See* Wolen, *supra* note 23, at 420.

[27] Abdul E. Mutlib, *Application of Stable-Labeled Compounds in Metabolism and in Metabolism-Mediated Toxicity Studies*, 21 CHEMICAL RES. IN TOXICOLOGY 1672, 1673 (2008).

[28] David Wade, *Deuterium Isotope Effects on Noncovalent Interactions Between Molecules*, 117 CHEMICO-BIOLOGICAL INTERACTIONS 191, 193 (1999). Kinetic isotope effects are possible for any isotope. *See id.* at 193-94. However, this Note is concerned with the kinetic isotope effect of deuterium

energy required to break a covalent bond to deuterium versus a covalent bond to hydrogen, and are expressed as a ratio of the rate of reaction for the protio molecule (k_H) over the rate of reaction for the deuterated molecule (k_D).[29] Deuterium isotope effects occur because of the significant mass difference between hydrogen and deuterium.[30] The C–D bond is ten times stronger than the C–H bond, making it more resistant to chemical or enzymatic cleavage.[31] If the cleavage of a C–H bond is implicated in the rate-determining step of a metabolic pathway, an overall decrease in metabolism will be observed when hydrogen is substituted with deuterium.[32] Therefore, the reduction in metabolism attributable to deuterium substitution extends the desired effects of a drug while retarding its undesirable effects.[33]

relative to its hydrogen isotope, and thus refers to this isotope effect as the deuterium isotope effect.

[29] *See id.* at 193. A covalent bond is formed by the sharing of two or more electrons between two atoms. OXTOBY & NACHTRIEB, *supra* note 22, at I-6.

[30] *See* Foster, *supra* note 18, at 4. Each atom of a covalent bond has a mass which contributes to the vibrational energy of the bond. *See* Foster, *supra* note 18, at 4; FRANCIS A. CAREY & RICHARD J. SUNDBERG, ADVANCED ORGANIC CHEMISTRY—PART A: STRUCTURE AND MECHANISMS 332 (5th ed. 2007). The energy required to vibrate the atoms (and thus break the covalent bond) is related to the mass of the atoms. *Id.* Greater energy is required to vibrate a heavier atom, such as deuterium, and therefore greater energy is required to break a C–D bond than a C–H bond. *Id.* Because deuterium is twice the mass of hydrogen, its kinetic isotope effect is greater than that observed for isotopes of other elements whose mass differs from the most abundant isotope by a smaller percentage. D.J. Kushner, Alison Baker & T.G. Dunstall, *Pharmacological Uses and Perspectives of Heavy Water and Deuterated Compounds*, 77 CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 79, 80 (1999).

[31] *See* Kushner, et al., *supra* note 30**,** at 80. Most of the hydrogen atoms on a molecule participate in a covalent bond (a mutual sharing of electrons) with a carbon (C) atom. Kushner, et al., *supra* note 30**,** at 80. Although there are many metabolic pathways which do not involve the cleavage of a C–H bond and therefore would not exhibit a kinetic isotope effect (for example, oxidation of nitrogen (N) to *N*-oxides), the cleavage of a C–H bond in favor of a more polar atom, such as oxygen (O), is a primary metabolic pathway. SILVERMAN, *supra* note 10, at 430.

[32] *See* Foster, *supra* note 18, at 4. The rate-determining step of a reaction is the step which is significantly slower than the other steps in a reaction process and therefore controls the overall rate of the process. *See* Foster, *supra* note 18, at 4; OXTOBY & NACHTRIEB, *supra* note 22, at I-18.

[33] Foster, *supra* note 18, at 4.

There are numerous examples of deuterium's effect on the metabolism of biologically active molecules. The anesthetic chloroform ($CHCl_3$) is metabolized in vivo to phosgene, a highly reactive alkylating agent.[34] Deuteration of chloroform to deuterochloroform ($CDCl_3$) decreases its metabolic rate, thereby reducing liver and lung toxicity in rats by five to seventy percent over chloroform.[35] Conversely, 1,2-dibromoethane ($BrCH_2CH_2Br$) is itself a DNA alkylating species, and the tetra-deuterated species $BrCD_2CD_2Br$ is indeed metabolized more slowly than the protio version.[36] However, the deuterated species actually causes more DNA damage than its protio counterpart because reduced metabolism prolongs the existence of the reactive species in the body.[37] Similarly, the anticonvulsive diazepam requires metabolic oxidation to its active form, oxepam, and deuteration therefore inhibits the anticonvulsive activity observed from administration of diazepam by preventing the production of the pharmaceutically active species.[38]

Although the deuterium isotope has been extensively used as a tool to identify metabolites and metabolic pathways,[39] it has not yet been incorporated into a clinical candidate.[40] One of the challenges of incorporating deuterium into a drug is the possibility of deuterium/hydrogen exchange within the physiological environment, eviscerating the effect of the compound.[41] Further, when deuterium retards metabolism at one site, a phenomenon called "metabolic switching" or

[34] *See* Mutlib, *supra* note 27, at 1680; Foster, *supra* note 18, at 31.

[35] Mutlib, *supra* note 27, at 1680.

[36] Mutilb, *supra* note 27, at 1679.

[37] Mutlib, *supra* note 27, at 1680. This example is one way in which metabolism is beneficial. Mutlib, *supra* note 27, at 1680. 1,2-Dibromoethane is not a substance which one ordinarily would ingest but is used for illustrative purposes. Mutlib, *supra* note 27, at 1680.

[38] Kushner, et al., *supra* note 30, at 83. A compound which is metabolized to an active species is also known as a prodrug. Foster, *supra* note 18, at 2.

[39] *See* Kushner, et al., *supra* note 30, at 83; Mutlib, *supra* note 27, at 1672.

[40] *See* Kushner, et al., *supra* note 30, at 85 (stating that, as of 1999, there was no deuterated drug on the market). *But see* Cathy O'Driscoll, *Heavyweight Drugs*, CHEMISTRY & INDUSTRY, Mar. 9, 2009, at 24, 25 (speculating that a commercial drug containing deuterium may be on the market in four or five years).

[41] *See* Foster, *supra* note 18, at 8 (arguing that where enzymes, receptors, or other macromolecules are involved, there is always the possibility of micro-environments in which deuterium-hydrogen exchange can be promoted).

"metabolic shunting" can occur where the suppression of one metabolic pathway promotes metabolism at another site.[42] For a deuterated clinical candidate to be successful, it must address the problems of biochemical deuterium exchange and metabolic switching. The "ideal starting point" in developing a deuterated drug, also referred to as an isotopolog, is to selectively deuterate a drug in clinical development which has a known metabolic profile.[43] Deuterated drugs of interest are those whose pharmacological or metabolic profiles differ from their protonated versions.[44]

Incorporating deuterium into novel compounds in an effort to mediate metabolism is a strategy which may find success in traditional drug design and development. Recently, two small pharmaceutical companies, CoNCERT Pharmaceuticals, Inc. in Lexington, MA and Auspex Pharmaceuticals in Vista, CA, have initiated drug development programs targeting deuterated analogs of prior art small molecules in an effort to improve their safety and efficacy by altering their metabolic profiles.[45] The

[42] *See* Foster, *supra* note 18, at 6; SILVERMAN, *supra* note 10, at 422 (deuteration at one site may change the partition between two metabolic pathways).

[43] Foster, *supra* note 18, at 2.

[44] *See* Kushner, et al., *supra* note 30, at 83. An example of the differences between an isotopolog and its protio version is shown in the clinical trial data of SD-254, an isotopolog of Effexor®. O'Driscoll, *supra* note 40, at 25. SD-254 is metabolized half as fast as Effexor®, and effective levels of the drug were maintained after twenty-four hours, substantially longer than that observed for the protio version. O'Driscoll, *supra* note 40, at 25. This difference in the pharmacokinetics of SD-254 may allow for the administration of a lower dose while maintaining the same effects, thereby decreasing the incidences of negative side-effects, which are usually dose-related. O'Driscoll, *supra* note 40, at 25.

[45] Between them, CoNCERT Pharmaceuticals and Auspex Pharmaceuticals have filed more than 300 patent applications and currently have two deuterated compounds in Phase I clinical trials, with a third anticipated to begin trials in 2009. O'Driscoll, *supra* note 40, at 25-26. Initial results from the clinical trials of Auspex's deuterated Effexor® and CoNCERT's deuterated Paxil® demonstrate the potential success of deuterating known drugs, as both trials exhibited a dramatic reduction in the metabolism of the deuterated agent. Amanda Yarnell, *Heavy-Hydrogen Drugs Turn Heads, Again*, CHEMICAL & ENGINEERING NEWS, June 22, 2009, at 36-38. On June 2, 2009, CoNCERT announced a $1 billion collaboration with GlaxoSmithKline in which the two companies will develop and commercialize deuterium-containing medicines.

issue of whether a deuterated analog of a prior art compound is obvious has not yet been presented to the courts. This Note surveys the courts' approaches to other obviousness challenges in the chemical arts in an attempt to discern how they will address the deuteration of known compounds in an obviousness inquiry. As outlined below, unexpected differences between the prior art and the deuterated compounds may be the determining factor in assessing whether such compounds are obvious in light of the prior art.

III. Obviousness Jurisprudence Under *Graham*[46] and *KSR*[47]

The obviousness requirement of 35 U.S.C. § 103 ensures that patent monopolies are only granted in exchange for disclosure of the invention. Thus, knowledge which is already in the public domain is not adequate consideration for a patent monopoly.[48] The seminal case on obviousness jurisprudence is *Graham v. John Deere Co.* in which the Supreme Court outlined four factual determinations necessary to the ultimate decision of obviousness.[49] The scope and content of the prior art are determined, the differences between the prior art and the claimed invention are ascertained, and the level of ordinary skill in the pertinent art is resolved.[50] Secondary considerations, such as evidence of commercial success, long-felt but unresolved needs, and failure of others are additional indicia of nonobviousness and are therefore also relevant to the inquiry.[51]

See Press Release, CoNCERT Pharmaceuticals, Inc., CoNCERT Pharmaceuticals and GlaxoSmithKline Form Alliance to Develop Novel Deuterium Modified Drugs (June 2, 2009), *archived at* http://www.webcitation.org/5kBHa1kqg. The GSK-CoNCERT partnership validates CoNCERT's deuteration strategy. *Id.* *See also infra* note 267, and related text discussing CoNCERT Pharmaceuticals.

[46] Graham v. John Deere Co., 383 U.S. 1 (1966).

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

[48] *Graham*, 383 U.S. at 6 (arguing that the public benefit of innovation through disclosure is inherent in the standard expressed by the Constitution).

[49] *Id.* at 11. The Court acknowledged in *Graham* that obviousness under § 103 was merely a codification of judicial precedent first announced in *Hotchkiss v. Greenwood*, which required "more ingenuity and skill than that possessed by an ordinary mechanic acquainted with the business." *Id*.

[50] *Id.* at 17.

[51] *Id.* at 17-18. *See also* Mary Ann Liebert, *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court*

Recently, the Supreme Court has further held in *KSR v. Teleflex* that the combination of known elements is likely to be obvious when it yields no more than predictable results,[52] and evidence of synergy among the combined elements provides strong support for a finding of nonobviousness.[53]

In an attempt to avoid the hindsight trap of obviousness, the Court of Appeals for the Federal Circuit promulgated the "teaching, suggestion, or motivation" ("TSM") test which requires evidence of motivation or suggestion in the prior art to make the claimed invention before finding the patent obvious.[54] Courts apply the TSM test when obviousness is premised on the teachings of multiple prior art references.[55] Where there is a market need and a finite number of identified, predictable solutions, a person of ordinary skill in the art has the requisite motivation to pursue the known options.[56] Further, a person of

Decision in KSR International Co. v. Teleflex Inc., 26 BIOTECHNOLOGY L. REP. 649, 651 (2008).

[52] KSR International Co. v. Teleflex, Inc., 127 S. Ct. 1727, 1739 (2007) (arguing that when a patent combines old elements with no change in their respective functions, it "diminishes the resources available to skillful men").

[53] *See id.* at 1740; William M. Atkinson & Joey H. Foxhall, *Stating the Obvious Gets Easier: The Supreme Court's* KSR *Decision*, 26 NO. 2 INTELL. PROP. L. NEWS. 1, 10 (2008) (arguing that *KSR* seems to require synergy among combined elements).

[54] *KSR*, 127 S. Ct. at 1734 (holding that "a patent claim is only proved obvious if 'some motivation or suggestion to combine the prior art teachings' can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art"). *See also* Steven J. Lee & Jeffrey M. Butler, *Teaching, Suggestion, and Motivation:* KSR v. Teleflex *and the Chemical Arts*, 17 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 915, 917 (2007) (intimating that the TSM test was promulgated to prevent hindsight-based obviousness); Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 STAN. TECH. L. REV. 2, 20 (2007) (arguing that motivation to combine prior art references is the first *Graham* factor).

[55] *See* Lee & Butler, *supra* note 54, at 915; D. Benjamin Borson, KSR v. Teleflex, Inc*.: The Supreme Court Reviews Obviousness*, 89 J. PAT. & TRADEMARK OFF. SOC'Y 523, 525 (2007) (stating that a person of ordinary skill in the art must not only have had motivation to combine prior art references but must have had the motivation to combine the prior art teachings in the particular manner claimed).

[56] *See* Furrow, *supra* note 1, at 309 (reasoning that an invention might be rendered obvious based on the obvious-to-try doctrine if the finite number of solutions yields predictable results); Liebert, *supra* note 51, at 660 (arguing

ordinary skill in the art would recognize that a technique which improves one device might be applied to similar devices in the same way, thereby supporting a finding of obviousness.[57] Finally and most importantly, motivation to invent need not be explicit but possibly implicit in the prior art or in the nature of the problem itself.[58]

To satisfy the motivation requirement, an inventor must have a reasonable expectation of success, because a person of ordinary skill in the art would only be motivated to invent if there was a probability that such effort would result in the claimed invention.[59] A reasonable expectation of success does not demand absolute predictability, but must be more than a general incentive to conduct research in that area.[60] An expectation of success is an objective standard applied to a person of ordinary skill in the art, for if the inventor's own expectations were the standard by which to measure patentability, nonobvious inventions would only result from serendipity rather than rational experimentation.[61]

A prima facie case of obviousness exists where the prior art provides the requisite motivation or suggestion to make the claimed invention, and the applicant has a reasonable expectation of success.[62] Once the United States Patent and

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that motivation to vary the prior art in a predictable manner may support a finding of obviousness).

[57] *See KSR*, 127 S. Ct. at 1740; Furrow, *supra* note 1, at 309.

[58] *See* Borson, *supra* note 55, at 535 (asserting that the Federal Circuit has stated that the requisite motivation may be found in prior art references or in the knowledge of a person of ordinary skill in the art that certain references or disclosures within those references are of special importance to the field); Spenner, *supra* note 3, at 503 (motivation may be implicit in the combined teachings of the prior art, the knowledge of one of ordinary skill in the art, the nature of the problem to be solved, the common knowledge, or the prior art as a whole).

[59] Darrow, *supra* note 54, at 33 (stating that motivation to combine references will only be found where there is a reasonable expectation of success).

[60] Trask, *supra* note 2, at 2635.

[61] *See* Trask, *supra* note 2, at 2651 (reasoning that the inventor must have possessed a subjective expectation of success, otherwise he would not have expended the time and effort involved in experimentation).

[62] *See* Lee & Butler, *supra* note 54, at 924 (stating that the requirements of a prima facie case of obviousness include: (1) some suggestion or motivation,

Trademark Office ("PTO") has concluded that the claimed invention is obvious, the burden shifts to the applicant to provide other evidence that the invention is nonobvious.[63] The applicant may rebut a prima facie case of obviousness by showing that the invention possesses unexpected properties or that the prior art teaches away from the invention.[64] Finally, evidence of unexpected results must be established by factual evidence and not by conclusory statements in the specification.[65]

Inherent in any obviousness analysis is the notion that an invention was the result of an "obvious-to-try" combination.[66] Obvious-to-try exists when a general disclosure stimulates some curiosity meriting further investigation but does not contain sufficient information to achieve the result.[67] Obvious-to-try is

either explicitly or implicitly, to modify the reference or combine the teachings of the references, (2) a reasonable expectation of success, and (3) some suggestion or teaching in the prior art for the claim limitations). *See* Lee & Butler, *supra* note 54, at 924; Harold C. Wegner, *Chemical and Biotechnology Obviousness in a State of Flux*, 26 BIOTECHNOLOGY L. REP. 437, 440 (2008) (arguing that prima facie evidence is limited to cases where the prior art has enough utility to provide motivation to create the invention); Darrow, *supra* note 54, at 43 (stating that the first three *Graham* factors establish prima facie obviousness).

[63] Liebert, *supra* note 51, at 663. *See also* Spenner, *supra* note 3, at 482 (stating that prima facie obviousness is a tool designed to shift the burden of proof to the applicant).

[64] *In re* Geisler, 116 F.3d 1465, 1468 (Fed. Cir. 1997); *see also In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988) (stating that there is always a possibility of unexpected results which would provide an objective basis for showing that the invention, though apparently obvious, was in fact not obvious in the law); Wegner, *supra* note 62, at 440 (stating that when a prima facie case of obviousness exists, the applicant must demonstrate actual differences between the claimed compound and the prior art such that the invention as a whole is nonobvious). *See also* Takeda Chem. Indus., Ltd. v. Mylan Labs., 417 F. Supp. 2d 341, 370 (S.D.N.Y. 2006) (stating that the prior art teaches away from the invention when "it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention," thereby supporting a finding of nonobviousness).

[65] *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). Mere improvement in an invention's properties does not always evidence unexpected results, but 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." *Id.* at 751.

[66] 3 Ann. Pat. Dig. § 18:22 (2008).

[67] *Id*.

most often implicated when it would be obvious to vary all parameters or possible choices until a successful result is obtained.[68] Because obvious-to-try depends on having a reasonable expectation of success,[69] an invention would not be rendered obvious-to-try if success was realized in spite of potentially infinite combinations of parameters.[70] Although the obvious-to-try analysis is merely one aspect of an obviousness inquiry and does not by itself dispose of the matter, it may have increasingly greater influence in obviousness challenges involving inventions consisting of combinations of known elements.

IV. Obviousness in the Chemical Arts

Although the *Graham* factors and the TSM test apply to all patents, these requirements have been tailored to address the specific issues within the chemical arts in part, because a chemical structure is merely a means of describing the compound and is not the invention itself.[71] Motivation to invent is often inherent in drug discovery because research necessitates making small modifications to chemical compounds and then studying the largely unpredictable biological results.[72] Further, many important discoveries are made during late-stage drug development after the initial patents have been filed or issued.[73] The patents which cover these "follow-on" discoveries are especially susceptible to obviousness challenges because the

[68] *Id*. *See also* Wegner, *supra* note 62, at 443; Christopher K. Dorsey, *Isn't it Obvious? How the USPTO has Changed its Evaluation of Patent Applications in Response to the* KSR *Decision*, 20 NO. 5 INTELL. PROP. & TECH. L.J. 12, 14 (2008) (stating that an invention is obvious to try when the inventor chooses from a finite number of identified, predictable solutions with a reasonable expectation of success).

[69] *See* Liebert, *supra* note 51, at 659; Wegner, *supra* note 62, at 443. *See also* Atkinson & Foxhall, *supra* note 53, at 10 (asserting that obviousness "might" be evinced under an obvious-to-try argument when expected results are achieved).

[70] Spenner, *supra* note 3, at 493. Indeed, the *KSR* Court resurrected the obvious-to-try analysis as evidence of a prima facie case of obviousness when there is sufficient motivation to solve a problem and there are a finite number of possible solutions. Trask, *supra* note 2, at 2648.

[71] Wegner, *supra* note 62, at 440 (reasoning that the two-dimensional structure does not translate to the three-dimensional structure itself).

[72] *See* Trask, *supra* note 2, at 2625.

[73] Furrow, *supra* note 1, at 277.

claimed inventions closely relate to subject matter protected by earlier patents.[74]

Inherent motivation to synthesize a chemical compound is premised on the expectation that similar chemical compositions will exhibit similar properties.[75] Thus, motivation in the chemical arts may come from the chemical composition itself.[76] In *Aventis Pharma Deutschland v. Lupin*,[77] the Federal Circuit considered the level of motivation required to support a finding of obviousness in the chemical arts.[78] The patent at issue claimed the drug ramipril[79] as a single isomer;[80] however, ramipril was actually synthesized as a mixture of two isomers which were identified but not separated.[81] The issue before the court was whether ramipril was obvious over the prior art which disclosed

[74] Furrow, *supra* note 1, at 277.

[75] *In re* Soni, 54 F.3d 746, 750 (Fed. Cir. 1995); *In re* Lalu, 747 F.2d 703, 706 (Fed. Cir. 1984). *See also* Wegner, *supra* note 62, at 440 (reasoning that the predictability of properties is presumed when a series is composed of hundreds or thousands of known molecules and therefore the motivation to make a compound may be implicit within that series).

[76] Lee & Butler, *supra* note 54, at 924. *See also* Spenner, *supra* note 3, at 489 (arguing that structural relationships may provide the motivation or suggestion to modify known compounds of desirable utility).

[77] 499 F.3d 1293 (Fed. Cir. 2007).

[78] *Id*. at 1300-01. Defendant Lupin appealed from a judgment of infringement in which the district court held, prior to the *KSR* decision, that there was an absence of "clear and convincing" motivation to make the claimed compound. *Id*.

[79] *Id.* at 1296. Marketed as Altace®, ramipril is an Angiotension-Converting Enzyme (ACE) inhibitor which prevents blood vessel constriction and is useful for treating high blood pressure. *Id.* at 1296.

[80] *Id.* at 1295. An isomer is a compound which contains the same atoms as another compound but bonded in a different configuration. *Id.* A stereoisomer is an isomer which contains an asymmetric carbon atom bonded to four different groups in which the atoms have the same connectivity, but differ with respect to their three-dimensional orientation. *Id.* The asymmetric carbon atom is called a stereogenic center. *Id*. Stereoisomers are designated as either *R* or *S* as determined by the groups directly bonded to the carbon atom. *Id*. The isomers of ramipril are all stereoisomers. *Id*.

[81] *Aventis*, 499 F.3d at 1298. Analogizing to the prior art, the applicants presumed that the observed biological activity was due to the presence of one of the two isomers and thus claimed that isomer "substantially free of other isomers." *Id.*

structurally similar compounds possessing similar activity,[82] and whether one of ordinary skill in the art would have been motivated to separate ramipril from the other isomers produced during the synthesis.[83]

The Federal Circuit applied the reasoning of the recently announced *KSR* decision and reversed the district court's holding that there must be clear and convincing evidence of motivation.[84] The court reiterated the *KSR* holding which forbade a rigid application of the TSM test, reasoning that the motivation need not come from an explicit teaching that the claimed compound will have a particular activity.[85] The court then stated that the claimed compound bears a sufficiently close relationship to prior art compounds to create an expectation that the new compound will have similar properties.[86] The court further asserted that if a desirable property of a mixture is known to be attributable to one of its components, one would expect the purified component to retain the same properties it exhibited in the mixture.[87] Therefore, ramipril's close structural similarity to known biologically active compounds, coupled with established

[82] *Id*. at 1296-97. ACE inhibitors were initially designed by making structural modifications to Brazilian Viper venom, which was known to reduce blood pressure. *Id*. at 1296. Enalapril, the immediate predecessor to ramipril, contained three stereogenic centers all in an *S* configuration. *Id*. at 1297. Ramipril contains the same three stereogenic centers, all in an *S* configuration, and two additional stereogenic centers. *Id*. Significantly, ramipril was synthesized as a mixture of stereoisomers. *Id*. The issue on appeal was whether the prior art, which disclosed active ACE inhibitors possessing the same three stereogenic centers in the same configuration, provided sufficient motivation to separate the active stereoisomer from the undesired stereoisomer. *Id*.

[83] Aventis Pharma Deutschland v. Lupin, 499 F.3d 1293, 1300 (Fed. Cir. 2007). Appellee's own prior patent application disclosed the separation of the isomers that, along with ramipril, were produced during the synthesis, stating that "[w]hen diastereomeric products result from the synthetic procedures, the diastereomeric products can be separated by conventional chromatographic . . . methods." *Id.*

[84] *Id.* at 1301.

[85] *Id*.

[86] *Id*.

[87] *Aventis,* 499 F.3d at 1301-02. It follows then, that, if upon separating the stereoisomers one was significantly more active or had a better profile than expected, the evidence might support a finding of nonobviousness based on the doctrine of unexpected results. *See id*.

techniques for isolating the pure isomer, provided sufficient motivation to synthesize ramipril as a pure isomer.[88]

Early stage drug discovery entails the identification of lead compounds from potentially hundreds or thousands of possibilities and thus generally lacks specific motivation or expectation of success.[89] Further, the prior art must suggest the specific chemical modifications necessary to achieve the claimed compound to satisfy the motivation requirement.[90] A reasonable expectation of success or measure of predictability varies by discipline, and the predictability of mechanical components is not the same as predictability of chemical modifications designed to yield biological results.[91] However, it is generally not possible to predict whether chemical compounds with apparent structural similarity will also possess similar biological properties, thereby potentially rendering the reasonable expectation of success requirement superfluous when applied to the chemical arts.[92]

In the chemical arts, a prima facie case of obviousness exists where the prior art compound is sufficiently close in structure to the claimed compound.[93] The appellant in *In re Dillon*[94] claimed the use and composition of tetra-ortho ester compounds as fuel additives to reduce the emission of solid particulates during fuel combustion.[95] It was undisputed that the tetra-ortho esters were a known class of compounds whose combination with hydrocarbon fuels was not shown in the prior art and whose use to reduce particulate emissions was not previously shown or suggested by any reference.[96] However, the

[88] *Id*. at 1302.

[89] Furrow, *supra* note 1, at 311.

[90] Spenner, *supra* note 3, at 490.

[91] *See* Trask, *supra* note 2, at 2664-5; Wegner, *supra* note 62, at 441 (reasoning that a higher degree of predictability arises when thousands of compounds have been made and characterized such that an unpredictable result of yesterday will yield a predictable result today).

[92] *In re* Grabiak, 769 F.2d 729, 731 (Fed. Cir. 1985).

[93] *See* Ortho-McNeil v. Mylan Labs, 348 F. Supp. 2d 713, 749 (N.D.W. Va. 2004) (stating that the prior art must motivate and reasonably suggest that the compound would exhibit its unique combination of properties); Lee & Butler, *supra* note 54, at 923; Darrow, *supra* note 54, at 29.

[94] 919 F.2d 688 (Fed. Cir. 1990) (en banc).

[95] *Id.* at 690.

[96] *Id.* at 691.

use of tri-ortho esters as fuel additives to prevent phase separation between fuel and alcohol co-solvents was already the subject of an existing patent, and the chemical equivalence between tri-ortho esters and tetra-ortho esters was demonstrated by another reference.[97] The PTO Board of Appeals rejected the claims as obvious based on the fact that there was close structural similarity between the tri-ortho and tetra-ortho esters and both the prior art and the applicant had used these compounds as fuel additives.[98]

The Federal Circuit, sitting en banc, held that structural similarity between the claimed and prior art compounds creates a prima facie case of obviousness where the prior art gives a reason or motivation to make the claimed compositions.[99] The burden then shifts to the applicant to prove that the compounds are not obvious by providing evidence that the claimed compounds possess unexpectedly improved properties that are not present in the prior art.[100] The court affirmed the decision of the Board because the applicant had failed to present any evidence or data that showed her compositions had properties not possessed by the prior art structures or that they possessed them to an unexpectedly greater degree.[101]

Thus, to rebut a prima facie case of obviousness, unexpected results must be substantial over the prior art and established by objective, factual evidence.[102] An unexpected property of a biologically active compound may not necessarily be therapeutic, but may instead be an improved pharmacokinetic profile, such as a decrease in toxicity or side effects or an increase in bioavailability, stability, or distribution within the body.[103] However, unexpected properties of a compound must be truly

[97] *Id.* Prior art references demonstrated that tri-orthoesters and tetra-orthoesters both participate in a similar type of reaction and are equivalent for practical use. *Id*. at 692.

[98] *In re Dillon*, 919 F.2d 688,692 (Fed. Cir. 1990) (en banc).

[99] *Id.* at 692.

[100] *Id.* at 692-93.

[101] *Id.* at 693. *See also In re* Davies, 475 F.2d 667, 670 (C.C.P.A. 1973) (holding that undisclosed evidence of unexpected results must "inherently flow" from what was disclosed in the specification).

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

[103] *See* Borson, *supra* note 55, at 541.

unexpected and not merely unknown or inherent properties of a structural series.[104] Therefore, because a compound and its properties are inseparable, an obviousness inquiry requires consideration of the claimed compound as a whole.[105]

Application of the obvious-to-try concept to the chemical arts occurs when a prior art compound is modified chemically to arrive at the claimed structure.[106] The pharmaceutical industry is disproportionately affected by an obvious-to-try standard because there may be many chemically similar compounds to those in the prior art which are obvious to try.[107] However, obvious-to-try does not typically apply when there is a large group of compounds from which to choose a lead molecule, such as the results from a high-throughput screening assay.[108] Further, invoking obvious-to-try for a chemical compound based on structural similarity to a prior art compound necessarily disregards the compound's associated properties and potentially viscerates the directive of evaluating the compound and its properties as a whole.[109]

V. Obviousness of Enantiomers

A. Introduction to Enantiomers

All organic compounds contain carbon atoms which are capable of participating in four covalent bonds with other atoms.[110] A carbon atom bonded to four different groups does

[104] *See In re* Wilder, 563 F.2d 457, 460 (C.C.P.A. 1977) (stating that, when a later compound which is structurally similar to the prior art possesses properties which the prior art unknowingly possessed by virtue of its structure, there are no unexpected results but just unknown results); *In re* Hoch, 428 F.2d 1341, 1344 (C.C.P.A. 1970) (holding that actual differences between the prior art and the claimed compound must be proven to rebut a prima facie case of obviousness).

[105] *Ortho-McNeil*, 348 F. Supp. 2d at 749.

[106] *See* Trask, *supra* note 2, at 2634.

[107] *See* Trask, *supra* note 2, at 2663. Many pharmaceutical agents result from the modification of known compounds in an effort to obtain more desirable properties. Dorsey, *supra* note 68, at 14.

[108] *See* Spenner, *supra* note 3, at 491.

[109] *See* Trask, *supra* note 2, at 2641.

[110] PAULA YURKANIS BRUICE, ORGANIC CHEMISTRY 203 (5th ed. 2007). The three-dimensional structure of a carbon atom bonded to four atoms is tetrahedral. *Id*.

not have a plane of symmetry, and is thus asymmetric.[111] A compound which contains at least one asymmetric atom is said to be "chiral"—a term of art that describes the property of "handedness"[112]—and therefore not superimposable on its mirror image.[113] A chiral compound and its mirror image are said to have an enantiomeric relationship to each other and are called enantiomers.[114] An equal mixture of enantiomers is termed a racemic mixture.[115]

Enantiomers share many of the same properties.[116] An enantiomeric pair exhibits the same solubility, melting and boiling points, and spectral data.[117] Because they have identical physical properties, enantiomers are difficult to separate and differentiate from each other.[118] Importantly, enantiomers differ in the way they interact with polarized light and are thus discernable by measuring the degree of rotation of polarized light.[119]

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[111] *Id.* at 203.

[112] ANDREW STREITWIESER, CLAYTON H. HEATHCOCK & EDWARD M. KOSOWER, INTRODUCTION TO ORGANIC CHEMISTRY 123 (1992). The term "chiral" is derived from the Greek word *cheir*, meaning "hand." BRUICE, *supra* note 110, at 202. Chiral objects are not super-imposable upon their mirror images, as demonstrated by the right and left hands, which are identical in all respects but which can not fit into the other's glove. STREITWIESER et al., *supra* note 112, at 123.

[113] *See* BRUICE, *supra* note 110, at 203. An asymmetric center is also called a "stereogenic" center. *See* BRUICE, *supra* note 110, at 203. A compound which has a plane of symmetry, or alternatively, has a superimposable mirror image, is called "achiral." *See* BRUICE, *supra* note 110, at 203.

[114] STREITWIESER et al., *supra* note 112, at 124. An enantiomeric pair of compounds has the same connectivity of atoms which differ only in the relative spatial arrangement of those atoms about the asymmetric carbon. *Id*.

[115] BRUICE, *supra* note 110, at 215.

[116] *See* BRUICE, *supra* note 110, at 212; STREITWIESER et al., *supra* note 112, at 126.

[117] *See* BRUICE, *supra* note 110, at 212; STREITWIESER et al., *supra* note 112, at 126.

[118] *See* BRUICE, *supra* note 110, at 233. An isolated, single enantiomer is said to be enantiomerically pure. ERNEST L. ELIEL & SAMUEL H. WILEN, STEREOCHEMISTRY OF ORGANIC COMPOUNDS 5 (1994).

[119] *See* STREITWIESER et al., *supra* note 112, at 126. Polarized light is normal light which has been filtered through a polarizer. BRUICE, *supra* note 110, at 212. The polarizer only permits light which oscillates in a certain plane to pass through. BRUICE, *supra* note 110, at 212. When polarized light passes through a solution containing an enantiomerically pure compound, the light

Enantiomers react equally with achiral reagents because they have the same chemical properties.[120] However, enantiomers react differently with chiral reagents because each reacting partner has at least one stereogenic center that, when combined, produces two complexes which are no longer mirror images of each other.[121] The human body is comprised of proteins which contain many stereogenic centers and are therefore chiral.[122] A receptor is a chiral protein which binds a particular molecule.[123] Because it is chiral, a receptor will bind one enantiomer preferentially over the other.[124] This receptor-substrate affinity is responsible for the physiological differences observed between enantiomers and is one reason why pharmaceutical drugs are often administered as a single enantiomer rather than as a racemic mixture.[125]

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emerges with its plane of polarization changed. BRUICE, *supra* note 110, at 212. One enantiomer will rotate the plane of polarized light clockwise (dextrorotatory) while its mirror image will rotate the plane of polarized light in the equal but opposite direction (counterclockwise, or levorotatory). BRUICE, *supra* note 110, at 212-13. A solution which contains equal amounts of both enantiomers (a racemic mixture or racemate) will not rotate plane polarized light because the effects from the separate enantiomers will cancel each other out. BRUICE, *supra* note 110, at 215.

[120] BRUICE, *supra* note 110, at 247.

[121] BRUICE, *supra* note 110, at 247. When a mixture of two enantiomers reacts with a reagent that contains a stereogenic center, the complex formed between the chiral reagent and each enantiomer is different. BRUICE, *supra* note 110, at 247. If the enantiomers are designated A and A* and the chiral reagent is designated B, the respective complexes formed by reacting the enantiomeric pair A and A* with B are AB and A*B. BRUICE, *supra* note 110, at 247. The result is two complexes which have different physical properties and are readily separable and distinguishable. BRUICE, *supra* note 110, at 247.

[122] BRUICE, *supra* note 110, at 247. All naturally-occurring proteins are enantiomerically pure because the amino acid building blocks that comprise proteins exist as single enantiomers. *See* ELIEL & WILEN, *supra* note 118, at 203. These proteins make up enzymes and receptors within the body which are responsible for a multitude of biochemical processes. BRUICE, *supra* note 110, at 247.

[123] BRUICE, *supra* note 110, at 249. *See also* Spenner, *supra* note 3, at 481.

[124] BRUICE, *supra* note 110, at 249. *See also* Darrow, *supra* note 54, at 7 (stating that one enantiomer may not fit as well into the active site of an enzyme as compared to its mirror image, leading to substantially different pharmacological and toxicological effects).

[125] BRUICE, *supra* note 110, at 249. An extreme example of the physiological differences between enantiomers is the case of Thalidomide.

B. Obviousness of Enantiomers over Prior Art Racemates[126]

Historically, most pharmaceutical drugs were prepared and marketed as racemic mixtures, in part due to a lack of understanding of the individual enantiomers' effects in the physiological environment.[127] However, in response to several cases where negative side effects were attributed to the undesired enantiomer,[128] the FDA now requires data pertaining to the individual enantiomers of a chiral drug.[129] In the past twenty years, several pharmaceutical companies have filed for and obtained patents covering single enantiomer versions of racemic drugs already approved and on the market.[130] When the

BRUICE, *supra* note 110, at 249. Thalidomide was prescribed for pregnant women in the middle of the 20th century to treat morning sickness and insomnia. BRUICE, *supra* note 110, at 249. Thalidomide contains one stereogenic center, but was produced and prescribed as a racemic mixture. BRUICE, *supra* note 110, at 249. When women who had been prescribed Thalidomide began to give birth to children with severe birth defects, it was discovered that one enantiomer was largely responsible for the birth defects while the other was largely responsible for the sedative effects. BRUICE, *supra* note 110, at 249. Another example of the difference between enantiomers is the respective scents of the enantiomeric pairs (*S*)-carvone (caraway) and (*R*)-carvone (spearmint), and (*S*)-limonene (lemon) and (*R*)-limonene (orange). ELIEL & WILEN, *supra* note 118, at 202.

126 A racemate is another term for a racemic mixture, or a mixture of equal amounts of each enantiomer. Spenner, *supra* note 3, at 481.

127 *See* SILVERMAN, *supra* note 10, at 147-48 (stating that the expense of separating enantiomers is prohibitive). In 1992, the FDA began requiring pharmaceutical companies to justify the need to market a drug as a racemate. SILVERMAN, *supra* note 10, at 148.

128 Thalidomide is one of the most notorious cases where the two enantiomers were shown to exhibit drastically different biological effects. *See supra* note 125 and accompanying text.

129 Darrow, *supra* note 54, at 8. Many have argued that the FDA requirement of single-enantiomer data provides sufficient motivation to separate and test the individual enantiomers absent any other motivation in the prior art. Spenner, *supra* note 3, at 514.

130 Darrow, *supra* note 54, at 13. Often, the company who owns the racemate patent is seeking to extend its patent protection by separately patenting the single enantiomer. Darrow, *supra* note 54, at 13. However, other companies may seek to leverage a competitor's product, thereby gaining entry into a new market. Darrow, *supra* note 54, at 13. Indeed, the pharmaceutical company Sepracor, Inc. has obtained patents on single-

racemate of a chiral compound is disclosed in the prior art, patent examiners and, ultimately, the courts must determine whether a separated and isolated enantiomer is obvious over its racemate.[131]

Although a court must not declare that a prima facie case of obviousness exists for an enantiomer over its prior art racemate in the absence of the *Graham* factual inquiries,[132] the structural similarities between a single enantiomer and its racemate are usually sufficient to establish a prima facie case.[133] There is inherent motivation to separate a racemate into its constituent enantiomers because generally one enantiomer will possess superior properties as compared to the racemate.[134] However, motivation to separate enantiomers is not a foregone conclusion. A reference which suggests that each enantiomer is equally responsible for the side effects or which indicates that the enantiomers are likely to interconvert vitiates any motive to separate the enantiomers.[135]

enantiomer versions of sixteen chiral drugs previously sold as racemates by other companies. Darrow, *supra* note 54, at 13. An example of a "racemic switch," where the racemate is switched for the active enantiomer, is the anti-ulcer drug omeprazole, marketed by AstraZeneca as Prilosec®. SILVERMAN, *supra* note 10, at 148. Shortly before the Prilosec patent expired, AstraZeneca was issued a patent for the *S* isomer, esomeprazole, now marketed as Nexium®. SILVERMAN, *supra* note 10, at 148.

[131] *See* Darrow, *supra* note 54, at 5 (stating that knowledge of the structure of one enantiomer (or its racemate) necessarily suggests the structure of the other).

[132] Spenner, *supra* note 3, at 502. Because *Graham* requires factual inquiries for each case, a court must not conclude a priori that a prima facie case exists for any compound. Spenner, *supra* note 3, at 502.

[133] Darrow, *supra* note 54, at 30. *See also* Spenner, *supra* note 3, at 511 (stating that a prima facie case of obviousness is made when the prior art racemate is disclosed in light of the general knowledge that racemates can be resolved into enantiomers which often possess different properties).

[134] *See* Spenner, *supra* note 3, at 486. Furrow, *supra* note 1, at 291 (stating that often, one enantiomer will possess promising efficacy and toxicity profiles while the other will be ineffective or highly toxic). *See also* Darrow, *supra* note 50, at 21 (reasoning that a person of ordinary skill in the art would be motivated to combine a reference disclosing a racemate with references indicating that single enantiomers may exhibit more desirable properties in an attempt to isolate the enantiomers).

[135] Darrow, *supra* note 54, at 24.

Because one enantiomer will generally exhibit superior activity over the racemate, an expectation of success usually accompanies efforts to separate enantiomers.[136] An expectation of success need not be absolute predictability, and is fulfilled by an expectation that the enantiomer will possess at least one significantly improved property.[137] However, even if there exists an expectation of improved properties for a single enantiomer, the enantiomer may not be obvious over its racemate if there is no disclosed means of resolution.[138] Indeed, the more difficult and nonobvious the separation of enantiomers, the more likely they are nonobvious over the racemate because there is no expectation of successful resolution.[139]

Even though a prima facie case of obviousness exists where there is inherent motivation to separate enantiomers combined with an expectation that one enantiomer will exhibit an improved pharmaceutical profile, evidence of unexpected results may still render an enantiomer nonobvious over its racemate.[140] Generally, the toxicity of the racemate is expected to fall between the toxicities of the individual enantiomers.[141] Further, the active enantiomer will typically exhibit only a two-fold increase in potency over the racemate.[142] A greater increase in potency over the racemate would be considered unexpected

[136] Darrow, *supra* note 54, at 51. A reasonable expectation of success is not negated by the fact that many enantiomers have failed to demonstrate improved clinical properties over their racemates. Darrow, *supra* note 54, at 58.

[137] Darrow, *supra* note 54, at 36.

[138] Darrow, *supra* note 54, at 56 (reasoning that the process for making the racemate does not make obvious a process for resolving the enantiomers); Spenner, *supra* note 3, at 513 (stating that there is no presumption that enantiomers are obvious over their racemates when the method of resolution is nonobvious).

[139] Spenner, *supra* note 3, at 489.

[140] Darrow, *supra* note 54, at 46. The most likely difference between the racemate and a single enantiomer may be the level of pharmacological activity. Darrow, *supra* note 54, at 46.

[141] Spenner, *supra* note 3, at 495.

[142] Spenner, *supra* note 3, at 495. *But see* Darrow, *supra* note 52, at 51 (arguing that generally one enantiomer will exhibit a much higher activity than the other, so superior activity for one enantiomer is expected).

and indicative of synergistic effects.[143] Alternatively, one enantiomer may affect the metabolism of the other by altering the bioavailability or toxicity profile of the other.[144] Therefore, it is difficult to extrapolate the properties of a racemate to the properties of the individual enantiomers.[145]

Evidence of nonobviousness must be based on actual evidence and not merely on attorney conjecture.[146] General assertions that enantiomer separation techniques are known or that one enantiomer would be expected to have a better profile are not based on evidence specific to the compound at issue.[147] These allegations are rebuttable with evidence of actual difficulty in separating the enantiomers and of the unexpected properties of the separated enantiomers.[148]

The unexpected properties of Plavix®, the dextrorotatory enantiomer of clopidogrel, ultimately rendered the compound nonobvious over its racemate.[149] Sanofi had previously developed a structurally similar compound which suffered from adverse side effects and they sought to improve on the structural class.[150] After synthesizing many racemic molecules, they

[143] Spenner, *supra* note 3, at 495. Such synergy might be the result of one enantiomer inhibiting the activity of the other, thereby preventing the desired pharmacological effect. Furrow, *supra* note 1, at 291.

[144] Furrow, *supra* note 1, at 291.

[145] *See* Darrow, *supra* note 54, at 31.

[146] *See* Forest Labs. v. Ivax Pharm., Inc., 501 F.3d 1263, 1268-69 (Fed. Cir. 2007).

[147] *Id.* at 1269. Forest, the owner of a patent covering the racemic antidepressant citalopram, was granted a patent on the dextrorotatory enantiomer of citalopram. *Id*. at 1266. Ivax challenged the validity of the patent, arguing that the enantiomer was obvious in light of the prior art racemate. *Id*. at 1269. Ivax maintained that enantiomers are known to be separable by routine methods and one of ordinary skill in the art would expect that one enantiomer would possess a better profile than the other. *Id*.

[148] *Id*. at 1269. The district court, with the Federal Circuit affirming, held that the difficulty of the separation and the unexpected properties of the dextrorotatory enantiomer rendered the enantiomer nonobvious in spite of the racemate. *Id*.

[149] Sanofi-Synthelabo, Inc. v. Apotex, Inc., 550 F.3d 1075, 1090 (Fed. Cir. 2008). Plavix® is an anti-thrombotic agent which inhibits the aggregation of platelets and is used to treat patients at risk for heart attacks and strokes. *Id*. at 1077.

[150] *Id*. at 1078.

attempted to separate the enantiomers of two compounds.[151] On separation, it was found that none of the separated enantiomers afforded any benefit over their respective racemates and the Sanofi scientists concluded that the resolution of enantiomers within that structural class was futile.[152]

Although none of the previously separated enantiomers had exhibited any improved properties over their racemates, the Sanofi scientists again attempted to separate the enantiomers of another promising compound, designated PCR 4099.[153] After many months filled with many experiments, the scientists were able to successfully separate the enantiomers.[154] Once separated, it was determined that the dextrorotatory enantiomer imparted all of the beneficial antiplatelet activity, while the levorotatory enantiomer imparted all of the neurotoxicity of the racemate.[155] This absolute stereoselectivity is extremely rare because the more potent enantiomer is usually also responsible for the adverse effects.[156]

On appeal, Apotex argued that it is well known that enantiomers can have different levels of biological activity.[157] Further, they argued that it would be obvious to separate the enantiomers and determine their properties even if the exact allocation of properties is unpredictable.[158] Apotex challenged the court's application of a reasonable expectation of success, stating that the expectation of success should refer to the success

[151] *Id*. at 1080-81.

[152] *Id*. at 1081.

[153] *Sanofi*, 550 F.3d at 1081.

[154] *Id*. There was testimony before the district court that there were at least ten separation techniques that might be tried, but that it was impossible to know which, if any, would work. *Id*.

[155] Sanofi-Synthelabo, Inc. v. Apotex, Inc., 550 F.3d 1075, 1081 (Fed. Cir. 2008).

[156] *Id*. Stereoselectivity describes the phenomenon where the activities of each enantiomer do not overlap, such that one enantiomer is exclusively responsible for the beneficial properties of the mixture and the other enantiomer is solely responsible for the negative properties observed in the mixture. *Id*. Typically, the more active enantiomer is also the more toxic enantiomer. *Id*.

[157] *Id*. at 1086. Specifically, Apotex asserted that one of ordinary skill in the art would expect a favorable allocation of properties between the enantiomers, thus rendering the separation of enantiomers obvious. *Id*.

[158] *Id*.

of the separation and testing of the enantiomer and not to the ultimate characteristics of the enantiomers.[159] The district court, with the Federal Circuit affirming, rejected this construction of the law, stating that the evidence overwhelmingly pointed to the unexpected characteristics of the dextrorotatory enantiomer, which was held to be nonobvious over the racemate.[160] Unlike the scientists in *Aventis* and contrary to the personal knowledge of the scientists at Sanofi, there was no expectation that either enantiomer would possess the desirable properties exhibited by the dextrorotatory enantiomer.[161] Therefore, the unpredictable properties of the resulting enantiomers, coupled with the uncertainty of the separation, ultimately rendered the dextrorotatory enantiomer of clopidogrel nonobvious.[162]

Whether an enantiomer is obvious over its racemate depends heavily on the doctrine of unexpected results. The properties of individual enantiomers cannot be presumed based on the properties of the racemate, because each enantiomer can

[159] *Sanofi,* 550 F.3d at 1087.

[160] *Id.* In addition to the unpredictable properties exhibited by the dextrorotatory enantiomer, the district court found that the separation of enantiomers was not routine. The district court noted the millions of dollars expended by Sanofi to develop the racemate prior to the separation of the enantiomers, which weighed against a finding of obviousness. *Id*.

[161] Sanofi-Synthelabo, Inc. v. Apotex, Inc., 550 F.3d 1075, 1087 (Fed. Cir. 2008).

[162] *Id*. at 1089. Additionally, an enantiomer may still be nonobvious despite the fact that the absolute stereochemical configuration of analogous, active compounds was known if the enantiomer exhibits an unexpected combination of properties. *See In re* May, 574 F.2d 1082, 1095 (C.C.P.A. 1978). The appellants in *May* sought to discover the structural features which imparted morphine's addictive properties, and had previously disclosed structurally similar racemic analogs of morphine. *Id*. at 1084. Further, the levorotatory enantiomers of the structural class were known to possess the analgesic effects of morphine. *Id*. at 1085. In addition to the expected analgesic effects, appellant's claimed levorotatory enantiomer showed none of the addictiveness that would normally be anticipated for this series. *Id*. at 1088. The court weighed the evidence of expected and unexpected results separately prior to the final determination of obviousness, stating that the mere fact that those skilled in the art would have expected the compound to exhibit analgesic activity did not create a non-rebuttable presumption of obviousness. *Id*. at 1093-94. The court then concluded that the unexpected non-addictive property of the claimed enantiomers, coupled with their analgesia, rendered the compounds nonobvious. *Id*.

exhibit significantly different and unexpected behavior.[163] If the desired properties are known to be attributable to a specific enantiomer, as was the case in *Aventis* where the activity was known to be derived from one of two stereoisomers in the mixture, the enantiomer may be obvious over its racemate despite the fact that it was not separated.[164] However, the notion of unexpected results also depends on the difficulty in separating enantiomers.[165] As the technology for the separation of enantiomers advances and separations become more routine, an enantiomer is more likely to be obvious over its prior art racemate despite exhibiting unexpected properties.[166]

VI. Obviousness of Analogs, Homologs, and Bioisosteres

Iterative structural modifications to known compounds generate new molecules known as analogs, which are used to probe the effects of structural changes on the biological activity of a molecule.[167] A homologous series is a group of compounds that differ by a constant structural unit, generally a CH_2 group.[168] Homologs are an important type of analog because their

[163] Darrow, *supra* note 54, at 31.

[164] Darrow, *supra* note 54, at 9-10.

[165] Darrow, *supra* note 54, at 10. *See also In re* Hoeksema, 399 F.2d 269, 273 (C.C.P.A. 1968) (stating that the process for making a claimed compound must be known or obvious to render the compound within the public domain, otherwise "the invention is nothing more than a mental concept expressed in chemical terms and formulae on a paper").

[166] *See* Spenner, *supra* note 3, at 483 (arguing that improvement of separation technologies decreases the innovation and creativity required to isolate enantiomers from their racemates); Darrow, *supra* note 54, at 16 (stating that an increase in knowledge of enantiomers decreases the "inventive genius" required to isolate a single enantiomer).

[167] *See* SILVERMAN, *supra* note 10, at 25. The term structure-activity relationship (SAR) is used to describe the relationship between the physiological action of a molecule and its chemical composition. SILVERMAN, *supra* note 10, at 21. Most drugs exhibit a high affinity for a receptor or enzyme, and are thus highly susceptible to small changes in chemical structure. SILVERMAN, *supra* note 10, at 21. Analogous compounds may be obtained through homologation, chain branching of aliphatic side chains, altering ring substitutions and substituents, ring-chain transformations, and isosterism. SILVERMAN, *supra* note 10, at 26-29.

[168] SILVERMAN, *supra* note 10, at 26. The compounds within a homologous series are called homologs. SILVERMAN, *supra* note 10, at 26.

properties are generally expected to trend in an increasing or decreasing manner along a continuum.[169] Analogs which incorporate bioisosteres contain groups which have similar chemical or physical characteristics and which produce similar biological properties.[170] Bioisosteric groups have been shown to be useful in attenuating toxicity or pharmacokinetics of a molecule in addition to altering its potency or activity.[171] Analogs, especially homologs and bioisosteres are particularly susceptible to obviousness challenges, because they are structurally similar to compounds which may exist in the prior art.[172]

A. Analogs

Takeda Chemical Industries, Ltd. v. Alphapharm Pty. Ltd.[173] serves to illustrate how courts apply the law of obviousness to analogs of prior art compounds.[174] Takeda had developed pioglitazone, a Type 2 diabetes drug and member of a class of drugs known as thiazolidinediones, or TZDs.[175] Pioglitazone was

[169] *See* SILVERMAN, *supra* note 10, at 26 (stating that a homologous series typically exhibits systematic increases or decreases in the biological properties of the molecules).

[170] *See* SILVERMAN, *supra* note 10, at 29. Formally, bioisosteres are substituents or groups on a molecule which exhibit similar physical or chemical characteristics. SILVERMAN, *supra* note 10, at 29. For the purposes of this Note, the term bioisostere will refer to compounds which incorporate bioisostere groups. SILVERMAN, *supra* note 10, at 29.

[171] *See* SILVERMAN, *supra* note 10, at 29. Examples of bioisosteric groups include those which have the same valence of electrons, as demonstrated by oxygen (O) and sulfur (S); the halides (F, Cl, Br, I); carbon (C) and silicon (Si); CH_2 and NH; etc. SILVERMAN, *supra* note 10, at 29.

[172] *See* Lee & Butler, *supra* note 54, at 924-25 (stating that positional isomers or homologs are sufficiently close in structure that there is a presumed expectation that such compounds possess similar properties).

[173] 492 F.3d 1350 (Fed. Cir. 2007).

[174] Takeda brought an infringement suit against Alphapharm, who countered that the patent was invalid under 35 U.S.C. § 103 as obvious. *Id*. at 1354.

[175] *Id*. at 1352. Patients with Type 2 diabetes produce insulin but are unable to effectively use the insulin produced. *Id*. The TZD drug class activates insulin receptors and enables glucose to enter the cell. *Id*. Takeda was the first to discover that the class of TZDs was useful in sensitizing muscle cells to insulin, allowing the body to more effectively use the insulin it produces. *Id*.

a close structural analog of TZD compounds which had existed in the prior art for several years.[176] Challenging the validity of Takeda's patent, Alphapharm asserted that pioglitazone was obvious in light of Takeda's previous patents and publications.[177]

At trial, the defendants argued that the prior art identified an analog of pioglitazone as a lead compound warranting further investigation, and it would have been obvious to make the structural modifications necessary to transform the prior art compound into pioglitazone.[178] The district court disputed Alphapharm's reasoning, stating that there was no motivation to synthesize pioglitazone or its analogs because the prior art taught away from the structural class by commenting on the adverse effects associated with that series.[179] The court

[176] *Id*. at 1357. Takeda had been issued a patent four years prior to the pioglitazone application which claimed a genus of TZDs encompassing "hundreds of millions of compounds." That patent specifically identified fifty-four compounds, including one referred to as "compound b." *Id*.

[177] *Takeda*, 492 F.3d at 1357. Takeda's prior patent disclosing "compound b" did not disclose experimental data or test results for any compounds. *Id*. However, the prosecution history disclosed test results for nine specific compounds, including "compound b," but never stated that those identified compounds were the best compounds. *Id*. Further, Takeda scientists published an article which disclosed 101 TZD compounds with accompanying efficacy data. *Id.* at 1358. The article did not present toxicity or side effect data, but did comment generally on these issues for particular compounds. *Id*. Specifically, the authors identified three compounds having favorable activity and toxicity profiles. *Id*. The article also stated that "compound b" showed increases in rodent body weight, a characteristic which was universally considered to be undesirable at the time. *Id*.

[178] *Id*. at 1357. Specifically, the defendants argued that one skilled in the art would have selected "compound b" for further modification and would have proceeded to modify it to eventually synthesize pioglitazone. *Id*. The defendants also asserted that any medicinal chemistry program would have synthesized all possible variations through processes known as "homologation" and "walking the ring," where side chains are extended by CH_2 units to probe the binding pocket and moved around the ring to identify their optimum location. *Id*. at 1359.

[179] Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd., 492 F.3d 1350, 1358 (Fed. Cir. 2007). The court further reasoned that there were thousands of different substituents that one of ordinary skill in the art could consider in modifying the prior art compounds. *Id*. The court then stated that even if one were to choose one of the identified structurally similar compounds, one would have been motivated to make radical changes to the structure in an effort to overcome the problems associated with the series. *Id*. at 1360.

reasoned that the prior art article evinced that its authors understood that simple homologation would not eliminate toxicity,[180] and even if one had made analogs of the prior art, toxicity problems would have been immediately apparent such that one would not have continued to pursue this series.[181] Despite rejecting the defendant's assertions that a prima facie case of obviousness existed,[182] the court further stated that there was compelling and conclusive evidence that pioglitazone's non-toxicity was unexpected.[183] Additionally, the evidence showed that pioglitazone, marketed and sold as ACTOS®, enjoys huge commercial success, thereby supporting a finding of nonobviousness.[184] Therefore, the court held pioglitazone to be nonobvious because one of ordinary skill in the art would not have had a resonable expectation that synthesizing a close structural analog of a prior art compound would have resulted in a non-toxic molecule suitable for development as a treatment for diabetes.[185]

B. Homologs

Novel members of a homologous series must possess some unexpected beneficial property not possessed by a homologous compound disclosed in the prior art to be

[180] *Id*.

[181] *Id*. at 1360.

[182] The defendants also asserted that, despite the fact that there was evidence that biological activity was unpredictable, the analogs were still obvious-to-try, and that anything was possible when modifying a compound. *Id*. at 1361. The court dismissed this argument, stating that the ultimate question was whether one skilled in the art would have had a reasonable expectation of success in synthesizing those analogs. *Id*. at 1360.

[183] *Id.* at 1361.

[184] *Takeda,* 492 F.3d at 1352. In 2003, ACTOS® held forty-seven percent of the TZD market and ten percent of the oral antidiabetic drug market, with sales in excess of $1.7 billion. *Id*. at 1353. There was further evidence that the TZD class of drugs revolutionized the treatment of diabetes and thus responded to a long-felt but unmet need in the market. *Id*. at 1352. Commercial success and the response to a long-felt but unmet need in the market are two of the *Graham* secondary considerations. Graham v. John Deere, 383 U.S. 1, 17-18 (1966).

[185] Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd., 492 F.3d 1350, 1362 (Fed. Cir. 2007).

considered nonobvious.[186] The appellants in *In re Hass* had claimed a series of compounds which were homologous to a prior art compound.[187] The examiner rejected the applicant's claims as unpatentable because they failed to establish that the prior art compound differed in its properties from other members of the series.[188] The appellants argued that they should not be required to present evidence of unexpected or unobvious properties because the novelty of their compounds should be sufficient for patentability.[189]

Affirming the examiner's rejection of the claims, the court stated that that the applicants did not provide evidence that the claimed compounds differed from the properties, qualities, and utility of the homologous prior art compound.[190] The court reasoned that chemists understood that members of a homologous series possess the same principal characteristics because, generally, the chemical and physical properties of the individual members vary gradually from member to member.[191] Further, the court stated that knowledge of the properties of one member of the series suggests to the chemist the properties of other members of the series.[192] Therefore, because appellants

[186] *In re* Hass, 141 F.2d 122, 125 (C.C.P.A. 1944). Although decided prior to the enactment of 35 U.S.C. § 103, *Hass* is informative for its factual circumstances because it was one of the first cases to address the patentability of homologs. *Id*. at 122.

[187] *Id*. The homologous series consisted of R = H, CH_3, C_2H_5, C_3H_7, etc. The compound where R = CH_3, 2-nitro-2-butene, was known in the prior art and thus excluded from the claim language, which read: "[n]itroolefins . . . wherein R is a member of the group consisting of hydrogen and an alkyl group having in excess of one carbon atom." *Id*.

[188] *Id*. at 124. The examiner stated that the applicants had not shown that the claimed compounds possessed any unobvious properties or utility, and instead relied solely on the novelty of the compounds. *Id*. at 123. The examiner noted that preparing additional members of a known homologous series is not inventive despite the fact that the new members of the series are technically new. *Id*.

[189] *Id*. at 125 (arguing that novel compounds tend to promote the progress of science and useful arts).

[190] *In re* Hass, 141 F.2d 122, 125 (C.C.P.A. 1944).

[191] *Id*.

[192] *Id*. The court reasoned that the applicants themselves took advantage of this assumption in their application, where they describe two representative members of the series but claim all members of the series. "Apparently, appellants were of opinion that as they had produced and

did not identify any unexpected properties not possessed by the prior art homolog, the other members of the homologous series were rendered obvious and unpatentable.[193]

C. Bioisosteres

A compound whose properties only differ from its bioisostere by a matter of degree is obvious under 35 U.S.C. § 103.[194] Appellant's application related to a method of treating human mental disorders by administration of the drug amitriptyline.[195] Amitriptyline was known in the prior art for its activity against the central nervous system, but was not known to be an antidepressant.[196] Another antidepressant in the prior art, imipramine, was structurally similar to amitriptyline and differed only in the substitution of an unsaturated carbon on imipramine with a nitrogen atom.[197] Further, a prior art reference suggested that amitriptyline should be clinically tested for depression because of the known similarities between the two compounds.[198]

At the time of the application, another prior art reference disclosed two compounds which were related to each other in the same manner as imipramine and amitriptyline.[199] In comparing the two compounds, it was noted that the pharmacological properties of chlorprothixene strongly resembled the properties

described two members of the homologous series covered by claim 1, it would not involve invention to produce the other members of the series covered by that claim." *Id*.

[193] *Id*. at 126. *Cf. In re* Papesch, 315 F.2d 381, 389 (C.C.P.A. 1963) (holding that the apparent obviousness of a compound may be overcome by evidence of unexpected properties, but where no such properties are shown to exist, it remains an obvious compound with obvious properties).

[194] *In re* Merck, 800 F.2d 1091 (Fed. Cir. 1986).

[195] *Id*. at 1092.

[196] *Id*. at 1094.

[197] *Id*. The prior art also defined isosteres as atoms in which the peripheral layers of electrons can be considered identical, as is the case for bioisosteres CH and nitrogen (N). *Id*. Compounds which contain isosteres and exhibit the same biological activity are termed "bioisosteric." *Id*.

[198] *In re* Merck, 800 F.2d 1091, 1095 (Fed. Cir. 1986).

[199] *Id*. Chlorpromazine differs from chlorprothixene by the replacement of a nitrogen atom in an aryl ring on chlorpromazine with a carbon atom. *Id*.

of chlorpromazine.[200] Based on this evidence, the applicant was denied a patent on the method of using amitriptyline as an antidepressant.[201]

Affirming the Board's decision, the Federal Circuit stated that a prima facie case of obviousness existed despite the fact that amitriptyline was not known as an antidepressant.[202] The court reasoned that the two compounds were so structurally similar that one skilled in the art would have expected amitriptyline to be useful in the treatment of depression.[203] Further, the court noted that the known bioisosteric replacement provided sufficient basis for an expectation of success required for a finding of a prima facie case.[204]

After concluding that a prima facie case of obviousness existed, the court then addressed appellant's evidence of unexpected results.[205] Merck argued that amitriptyline was an unexpectedly more potent sedative and stronger antidepressant than imipramine.[206] However, the court rejected this evidence as unexpected, stating that the evidence showed that the differences between imipramine and amitriptyline were not that unexpected.[207] In support of its conclusion, the court stated that amitriptyline was a known sedative and that all antidepressants with the same general structure showed sedative and anti-cholinergic properties.[208] The court concluded that the alleged difference in properties between amitriptyline and imipramine

[200] *In re* Merck, 800 F.2d 1091, 1095 (Fed. Cir. 1986). The reference stated that it was expected that the two compounds would show great similarity in properties because of the isosteric replacement of the nitrogen atom with the unsaturated carbon atom. *Id*.

[201] *Id.* at 1093-94. The Board of Patent Appeals affirmed the examiner's denial of a patent, reasoning that one of ordinary skill in the art would have expected amitriptyline to be useful as an antidepressant in light of both the prior art and the use of bioisosteres in medicinal chemistry. *Id*.

[202] *Id*. at 1096.

[203] *Id*. The expectation that amitriptyline would be an effective antidepressant was implicitly suggested by the prior art. *Id.* at 1097.

[204] *In re* Merck, 800 F.2d 1091, 1097 (Fed. Cir. 1986). The court stated that an expectation of success does not mandate absolute predictability but only a reasonable expectation that a beneficial result will be achieved. *Id*.

[205] *Id.* at 1098.

[206] *Id.* at 1098 (Fed. Cir. 1986).

[207] *Id*.

[208] *In re* Merck, 800 F.2d 1091, 1097 (Fed. Cir. 1986).

was a matter of degree rather than kind.[209] Therefore, the results showing the differences between the two compounds were not truly unexpected, and did not rebut the prima facie case of obviousness.[210]

Analogs, homologs, and bioisosteres all bear some structural similarity to prior art compounds. However, whether they are obvious depends on the degree of predictability and ultimate allocation of their properties. The structural similarity of analogs, homologs, and bioisosteres to the prior art suggests that the compounds would possess similar properties, thereby satisfying the requirements for prima facie obviousness. When analogs or bioisosteres exhibit unexpectedly different properties from those of the prior art compound, the analogs or bioisosteres may be unobvious precisely because their structural similarity to the prior art would imply otherwise.

VII. Obviousness of Formulations

Once a pharmaceutical drug has been developed, it must be formulated[211] to ensure bioavailability and solubility in the bloodstream.[212] Although the chemical structure of a drug is the biologically active entity, the formulation of a pharmaceutical can substantially improve the clinical profile by, for example, increasing efficacy.[213] Pharmaceutical companies usually desire an oral formulation because it is the most convenient form for patients.[214] Often a pharmaceutical company will continue to optimize the formulation of a compound even after the initial patent application and seek to protect the optimized formulation

[209] *Id.* at 1099. Further, the court noted that amitriptyline was only somewhat more effective as an antidepressant than imipramine. *Id*.

[210] *Id.* at 1099.

[211] Formulation is the delivery mechanism for active pharmaceutical ingredients. For example, an oral formulation most often requires that the drug be made into a capsule or tablet which can be swallowed by the patient. Other formulation methods include solutions which are injectable or administered through an IV, lotions which are absorbed through the skin, or inhaled therapies which are absorbed in the lungs.

[212] Bayer Schering Pharma A.G. v. Barr Labs. Inc., No. 05-cv-2308, 2008 WL 628592, at *1 (D.N.J. Mar. 3, 2008), *aff'd*, 575 F.3d 1341 (Fed. Cir. 2009).

[213] *See* Furrow, *supra* note 1, at 295. Formulations are directed at altering the physical properties of the active pharmaceutical itself. *Id*. at 315.

[214] *Bayer*, 2008 WL 628592, at *1.

as a separate invention.[215] In these cases, courts must address whether a new formulation is obvious over the parent compound or another formulation previously disclosed in the prior art.[216]

Plaintiffs in *Bayer v. Barr Labs.* developed a female contraceptive known as drospirenone, currently marketed as Yasmin®.[217] Because the scientists desired an oral formulation, research into potential formulations began with studies to discover drospirenone's stability to acid.[218] The initial studies indicated that drospirenone degraded upon exposure to acid,[219] and the Bayer scientists proceeded with the development of an enterically coated tablet to avoid a substantial loss in bioavailability.[220] After the enteric tablet of drospirenone showed varying success among test subjects in a series of small

[215] *See, e.g.,* U.S. Patent No. 4,129,564 (filed Nov. 11, 1977) (issued Dec. 12, 1978) (protecting the composition and synthesis of a class of compounds, of which drospirenone is a member); U.S. Patent No. 6,787,531 (filed Aug. 31, 2000) (issued Sept. 7, 2004) (protecting the micronization of drospirenone).

[216] *See Bayer*, 2008 WL 628592, at *1.

[217] *Id*. at *1. The patent protecting drospirenone as a composition of matter was issued in 1978. *Id*. at *6. In April 1983, Bayer decided to proceed with the development of drospirenone and began researching possible formulations to be used in clinical trials. *Id*. at *6-7. Upon discovering a more preferred formulation of drospirenone, Bayer filed for another patent protecting the new formulation. *Id* at *1. Bayer sued Barr for infringement of its patent, and Barr countered that the formulation patent was obvious in light of the prior art. *Id*.

[218] Bayer Schering Pharma A.G. v. Barr Labs. Inc., No. 05-cv-2308, 2008 WL 628592, at *1, *1 (D.N.J. Mar. 3, 2008), *aff'd*, 575 F.3d 1341 (Fed. Cir. 2009). The stability of drospirenone in hydrochloric acid was used to approximate the acidic environment of the stomach. *Id*. An oral drug must be capable of withstanding the acidic gastric juices in the stomach without degradation to be viable for oral formulation. *Id*.

[219] *Id*. In fact, fifty percent of the drospirenone sample was isomerized to its inactive isomer within forty-five minutes. *Id*. Drospirenone's apparent instability to acid was interpreted by the Bayer scientists to mean that a tablet containing drospirenone would dissolve and degrade in a patient's stomach acid before being absorbed into the bloodstream. *Id*.

[220] *Id*. at *7. An enteric coating is a pH sensitive film applied to a tablet which prevents the tablet from dissolving in the stomach acid. *Id*. at *3. Once the tablet passes from the stomach into the intestines, where the environment is less acidic, the tablet dissolves and releases the drug. *Id*. Enteric coatings are used both to prevent the drug from degrading in the acidic environment of the stomach and to prevent stomach irritation. *Id*.

clinical trials,[221] the Bayer scientists revisited the formulation of drospirenone in an effort to determine the extent to which its bioavailability was diminished in vivo.[222] Towards that end, the Bayer scientists used a non-coated, immediate release tablet and discovered that drospirenone did not isomerize and was superior to the enteric coated tablet in all respects.[223] In 2000, twenty-two years after the first issued patent on drospirenone, Bayer filed a patent claiming a micronized formulation of the combination drospirenone and ethinylestradiol.[224]

In holding that the patent was obvious and invalid, the district court noted that drospirenone was known in the prior art at the time of the patent application and micronization was a well-known formulation technique for poorly soluble drugs.[225] Specifically, the court stated that a person of ordinary skill in the art would have tested drospirenone in both in vivo and in vitro experiments to assess bioavailability because in vitro experiments are not always predictive of in vivo results.[226]

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[221] *Id*.

[222] *Bayer,* 2008 WL 628592, at *8-9. The Bayer scientists had originally only tested the stability of drospirenone in vitro and had not determined that drospirenone was in fact unstable in an organism. *Id*.

[223] *Id*. at *9. The results indicated that the non-coated tablet was absorbed more rapidly than the enteric coated tablet and exhibited less inter-patient variability. *Id*. Further, the non-coated tablets had the same bioavailability as the enteric coated tablet, and the enteric coated tablets were thereafter abandoned. *Id*.

[224] Bayer Schering Pharma A.G. v. Barr Labs. Inc., No. 05-cv-2308, 2008 WL 628592, at *1, *12 (D.N.J. Mar. 3, 2008), *aff'd*, 575 F.3d 1341 (Fed. Cir. 2009). Micronization is a formulation process whereby a drug particle is reduced in size, increasing its surface area and solubility in the stomach. *Id*. at *3. Ethinylestradiol is an orally active synthetic derivative of estradiol, a female sex hormone, a common component of female contraception. *Id*.

[225] *Id*. at *37. Bayer argued that the prior art taught away from micronizing acid-sensitive drugs like drospirenone because a reduction in particle size, while increasing dissolution rates, also increases the rate of degradation. *Id*. at *23. Dissolution is the process by which drug particles are solubilized in the gastrointestinal tract. *Id*. at *3.

[226] *Id*. at *22. The Bayer scientists initially only tested drospirenone in vitro and concluded based on those experiments that drospirenone was significantly prone to isomerization and degradation. *Id*. The court noted that a careful experimentalist would have tested drospirenone in both experiments before relying on in vitro data. *Id*. If drospirenone had been initially tested in vivo, it would have been apparent that it did not degrade and was viable as an

Further, the court observed that micronization generally improves the dissolution of a poorly soluble drug because the reduction in particle size increases the surface area of the drug, an important factor in solubility.[227] Finally, the court compared drospirenone to progesterone, another sex hormone which is not very soluble in water but which was found to be more bioavailable in a micronized form rather than an enteric coated tablet.[228]

The obviousness of a pharmaceutical formulation depends on the degree of difference between the claimed subject matter and the prior art. The combination of a known formulation and a prior art compound is precisely the sort of obvious combination that the *KSR* Court cautioned against.[229] Combining a known formulation and a known compound is likely to be obvious when the mixture yields predictable results.[230] Thus, a new formulation of a known compound must possess unpredictable and unexpected properties to survive an obviousness challenge under *KSR*.[231] Therefore, the micronized formulation of drospirenone was held to be obvious because its stability in acid was not unexpected in light of evidence that micronization can increase the bioavailability of insoluble, acid-sensitive drugs.[232]

oral tablet, thus preventing several years spent developing the enteric coated tablet. *Id*.

[227] *Id*. at *23. The court stated that the first step when formulating a poorly soluble drug is to micronize it to improve its dissolution rate. *Id*.

[228] *Bayer*, 2008 WL 628592, at *24.

[229] *See* KSR v. Teleflex, 127 S. Ct. 1727, 1739 (2007).

[230] *Id.*

[231] *Id*. *Cf*. Alza Corp. v. Mylan Labs., Inc., 388 F. Supp. 2d 717 (N.D.W. Va. 2005) (holding that an extended release form of oxybutynin, a urinary incontinence drug prescribed since the 1970's and identified as one of two highly soluble genitourinary smooth muscle relaxants, was obvious in light of the prior art which disclosed the application of extended release formulations to highly soluble drugs); Merck & Co. v. Teva Pharmaceuticals USA, Inc., 395 F.3d 1364 (Fed. Cir. 2005) (holding that a once-a-week dosing schedule of Fosamax®, a treatment for osteoporosis, was obvious in light of the prior art which suggested that a once-weekly dose at seven times the daily prescribed amount was as effective as seven daily doses despite the fact that incidences of esophageal injury decreased and patient compliance increased).

[232] *See generally Bayer*, 2008 WL 628592.

VIII. Obviousness of Salt Forms

Because organic compounds are not always soluble in water and orally administered drugs require some measure of water solubility, many pharmaceutical agents are marketed as salt forms.[233] A salt form generally possesses different physical properties than the corresponding parent compound, including improved chemical stability, crystalline forms, and improved solubility.[234] When a pharmaceutical company initially patents a composition of matter, it often utilizes a Markush group of pharmaceutically acceptable salts in addition to claiming the parent compound.[235] In the event that problems arise in development, a pharmaceutical company will seek alternative salt forms with better properties.[236] If the new salt form is not specifically claimed in the previous composition of matter patent, a patentee may attempt to file an application covering the new salt form.[237] Thus, a question of obviousness arises when an applicant seeks to patent a new salt form in light of the prior art parent compound.[238]

The appellee in *Pfizer, Inc. v. Apotex, Inc*. was the assignee of a patent covering amlodipine for the treatment of hypertension and ischemia.[239] Despite having excellent properties for capsule production,[240] amlodipine maleate

[233] *See* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1353 (Fed. Cir. 2007). Salts are formed by combining an acid with a base. *Id*. Salt forms improve bioavailability of drugs by increasing their solubility. *Id*.

[234] *Id*. at 1354.

[235] *See id*. at 1353 (listing hydrochloride, hydrobromide, sulfate, phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, and gluconate as those salts specifically claimed by Pfizer in its patent covering amlodipine).

[236] *Id*. at 1354.

[237] Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1353 (Fed. Cir. 2007).

[238] *Id*. at 1352.

[239] *Id.* at 1353. Pfizer sued Apotex for infringement of its patent and Apotex defended on the grounds that Pfizer's patent was obvious over the prior art. *Id*. at 1352. The amlodipine besylate salt is marketed as Norvasc®. *Id*.

[240] *Id at 1353*. In patents, salts are referred to as either acid addition (salts formed between a basic drug and an acid) or base addition salts (salts formed between an acidic drug and a base). Several acid addition salts were used to screen for the optimal salt form of amlodipine, including maleate, fumarate, salicylate, hydrochloride, and mesylate (or methane sulfonate). The maleate form was selected for development. *Id*.

possessed undesirable properties when compressed into a tablet.[241] The besylate salt[242] was thereafter identified as having superior properties to the maleate salt in its processing characteristics, including non-stickiness, and stability.[243] Pfizer then sought, and was granted, patent protection for the besylate salt of amlodipine.[244]

Vacating the district court's opinion upholding the patent's validity, the Federal Circuit held that the besylate salt was obvious based on a prior art reference which listed fifty-three FDA-approved acid addition salts, one of which was benzene sulfonate.[245] The Federal Circuit stated that one of ordinary skill in the art would have been motivated to test the besylate salt because there was ample evidence in the prior art that a besylate salt was a suitable salt form.[246] The court also noted that Pfizer was the assignee of a patent which disclosed a besylate salt form of a pharmaceutical composition having excellent physicochemical properties.[247]

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[241] Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1353-54 (Fed. Cir. 2007). Amlodipine maleate exhibited chemical instability and stickiness of the tablet blend. *Id*. Chemical instability refers to the resistance of the drug to chemical degradation. *Id*. at 1354. Stickiness refers to the drug's adherence to the manufacturing equipment, such as the tablet press. *Id*. The Pfizer scientists predicted that the capsule form of the maleate salt had a shelf life of three years, whereas the tablet form of the maleate salt was not suitable for commercialization. *Id*.

[242] *See id.* at 1353. The besylate salt is also referred to as the benzene sulfonate salt. *Id.* at 1353 n.1.

[243] *Id.* at 1354.

[244] *Id.*

[245] Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1363 (Fed. Cir. 2007). The district court had concluded that the list of FDA-approved salt forms did not instruct the person of ordinary skill in the art to create the besylate salt because of its infrequent use. *Id*. at 1355. The reference listed besylate salt as having been used in 0.25% of pharmaceutical preparations through 1974, the date of publication. *Id*. The district court noted that the examiner must have considered the reference because it was disclosed in the prior patent application but nonetheless found that the claims were nonobvious in spite of the reference. *Id*. at 1356.

[246] *Id.* at 1363. The Federal Circuit stated that one of ordinary skill in the art would have considered benzene sulfonate because of its known acid strength, solubility, and other chemical characteristics reported in the literature. *Id*. Further, prior art patents disclosed the use of benzene sulfonate as a suitable acid addition salt. *Id*.

[247] *Id*.

The court then addressed Pfizer's reasonable expectation of success, dismissing the notion of unpredictability as to whether a salt would form and what its exact properties would be as evidence of nonobviousness.[248] The court stated that a rule of law which equated unpredictability with patentability risked rendering patentable all new salt forms "simply because the formation and properties of each salt must be verified through testing."[249] Thus, the court maintained that there was an expectation of success that the salt would form and would work for its intended purpose.[250]

Finally, the court held that Pfizer failed to offer evidence of unexpected results.[251] The court rejected Pfizer's assertions that the besylate salt was unique in that it exhibited good stability, processability, and non-hygroscopicity,[252] and it was unexpected that one salt would possess all of these "outstanding" features.[253]

[248] *Id*. at 1364. The court stated that obviousness cannot be avoided by showing that there was some degree of unpredictability in the art as long as there was a reasonable probability of success. *Id*. *But see* Sanofi-Synthelabo, Inc. v. Apotex, Inc., 550 F.3d 1075, 1089 (Fed. Cir. 2008) (asserting unpredictability as to whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination and stating that Sanofi presented evidence that the prior art taught away from using sulfuric acid in salt formation).

[249] Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007). The court concluded that predictability could not be the proper standard by which to measure obviousness because the expectation need only be reasonable, not absolute. *Id*.

[250] *Id*. *But see* Wegner, *supra* note 62, at 452 (stating that the majority only considered the *therapeutic activity* of amlodipine in concluding that the salt form was obvious, as opposed to consideration of the invention *taken as a whole* which showed greatly improved physical properties of stability, solubility, non-hygroscopicity, and processability over the prior art, the absence of which would have prevented successful commercialization of the product).

[251] Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1371 (Fed. Cir. 2007) (stating that any superior property must be unexpected to be considered evidence of nonobviousness, and all the evidence presented by Pfizer was what the skilled artisan would have expected).

[252] Hygroscopicity refers to the ability of a compound to absorb water from the air, rendering it sticky.

[253] *Pfizer v. Apotex,* 480 F.3d 1348 at 1371. Pfizer further argued that the identification of a salt with such an array of favorable characteristics would require extensive experimentation because each salt "imparts unique

The court reasoned that Pfizer merely engaged in routine testing to optimize the selection of a known and suggested pharmaceutically acceptable salt to "ease its commercial manufacturing and marketing of the tablet form of the therapeutic amlodipine."[254]

The obviousness of salt forms depends on the predictability of the properties of the resulting drug. When a prior art compound is combined with FDA-approved acids sufficient to produce addition salts and yielding no more than predictable results, the chemical entity is likely to be obvious and unpatentable. However, the compound may not be obvious where the salt form exhibits unexpected properties or where the prior art teaches away from the specific acid addition salt.

IX. Obviousness of Deuterium Incorporation into Prior Art Structures

For years scientists have sought to influence drug metabolism in an effort to improve the profiles of drug candidates.[255] Many approaches are designed to change the physical topology of the labile site by crowding out metabolic enzymes.[256] Other approaches have targeted the electronic characteristics of the labile sites in an effort to diminish the enzyme's affinity for the site.[257] A common example is the use of

properties to the parent compound," thereby showing that the unique combination of properties of amlodipine besylate was unobvious. *Id*. at 1355-56.

[254] *Id*. The court stated that creating a product which is more desirable for manufacturing or cost purposes to enhance commercial opportunities is founded in common-sense and therefore not patentable. *Id*.

[255] *See* Jing Lin, et al., *The Role of Absorption, Distribution, Metabolism, Excretion and Toxicity in Drug Discovery*, 3 CURR. TOPICS IN MED. CHEM. 1125, 1125 (2003) (stating that poor pharmacokinetic properties is one of the major barriers preventing drugs from reaching the market). *See also supra* notes 15-21 and accompanying text.

[256] GARETH THOMAS, MEDICINAL CHEMISTRY 472 (2d ed. 2007). An example is the substitution of a methyl (CH_3) group for the more sterically-hindered *tert*-butyl ($(CH_3)_3C$) group. *Id*.

[257] *See* SILVERMAN, *supra* note 10, at 29 (listing fluorine (F) as an isostere of hydrogen (H)). *See also* B. Kevin Park & Neil R. Kitteringham, *Effects of Fluorine Substitution in Drug Metabolism: Pharmacological and Toxicological Implications*, 26 DRUG METABOLISM REV. 605, 610 (1994) (stating that an electronegative atom such as fluorine (F) near a metabolically labile site can

fluorine to block metabolism at a C–H bond.[258] However, fluorine is not an innocuous atom and can significantly affect the physical properties of the neighboring atoms.[259] Nevertheless, these approaches, while successful at decreasing metabolism at the intended site, either introduce additional potential sites of metabolism,[260] dramatically alter the overall properties of the molecule, or both.[261]

Deuterium incorporation is the latest innovative method of controlling metabolism through the modification of chemical

alter drug metabolism through inductive (through-bond) effects or conformational and electrostatic (through-space) effects).

[258] *See* Park & Kitteringham, *supra* note 257, at 607. Fluorine can be substituted for hydrogen without introducing any major steric changes. Park & Kitteringham, *supra* note 257, at 607. The C–F bond is one of the strongest bonds known in organic chemistry, and is therefore more stabile than the C–H bond. Park & Kitteringham, *supra* note 257, at 608. Thus, the C–F bond will be more resistant to cleavage than the corresponding C–H bond because of its increased bond strength. Park & Kitteringham, *supra* note 257, at 607.

[259] *See* Park & Kitteringham, *supra* note 257, at 607. Fluorine is the most electronegative element in the periodic table. Park & Kitteringham, *supra* note 257, at 607. Electronegativity is a measure of an element's ability to attract or hold onto electrons. STREITWIESER et al., *supra* note 112, at 160. The strong attraction between fluorine's positively charged nucleus and its electrons explains why fluorine, which is approximately 19 times heavier than hydrogen, is roughly the same size. Park & Kitteringham, *supra* note 257, at 607. The presence of fluorine on a molecule can alter a molecule's lipophilicity or hydrogen-bonding character because fluorine is capable of acting as a hydrogen-bond acceptor. Park & Kitteringham, *supra* note 257, at 608-09. Scientists have leveraged fluorine's ability to alter a drug's physical properties to effect beneficial changes in electron density at a given molecular site. Park & Kitteringham, *supra* note 257, at 610.

[260] Increasing steric crowding around a metabolically labile site introduces additional functional groups which may themselves be metabolized. *See* Foster, *supra* note 18, at 5 (stating that the introduction of an alkyl group may create new possibilities for metabolism and significantly change lipophilicity, and the introduction of fluorine may markedly modify the character of neighboring functional groups).

[261] For example, substituting hydrogen for fluorine in a molecule may alter the drug's dipole moment, pK_a, and the overall reactivity and stability of neighboring functional groups. Park & Kitteringham, *supra* note 257, at 607. Fluorine is also capable of undergoing elimination during metabolism due to the fluoride ion's stability as a leaving group. *Id*. at 609.

structures.[262] The substitution of deuterium for hydrogen at a metabolically labile site blocks metabolism of that site by inhibiting C–H bond cleavage.[263] Because of the kinetic isotope effects exhibited by deuterated structures,[264] deuterated compounds often demonstrate improved metabolic profiles over the corresponding protio versions, thereby potentially decreasing side effects and adverse events associated with the parent.[265] However, deuterium incorporation will only inhibit metabolism at C–D sites on the molecule and does not affect other metabolic pathways.[266]

Although deuteration is a technique which may be utilized in any drug development program, recently small pharmaceutical companies have applied for patent protection covering deuterated analogs of FDA-approved drugs and drugs that are currently in clinical trials.[267] These new chemical entities, or

[262] *See* Foster, *supra* note 18, at 5. As noted above, deuterium is a surrogate for hydrogen because of its nearly identical size and similar chemical reactivity. *See supra* notes 22-27 and accompanying text.

[263] *See* Michael B. Fisher, Kirk R. Henne & Jason Boer, *The Complexities Inherent in Attempts to Decrease Drug Clearance by Blocking Sites of CYP-Mediated Metabolism*, 9 CURRENT OPINION IN DRUG DISCOVERY & DEVELOPMENT 101, 101 (2006). Metabolism by the cytochrome P-450 (CYP) enzyme superfamily is a major mechanism of drug clearance from the body. *Id*. CYP's oxidize a C–H bond via insertion of oxygen into the bond, yielding C–O–H. *Id*. The increased strength of the C–D bond as compared to the C–H bond inhibits oxidation and therefore prolongs the existence of the active drug in the body. Foster, *supra* note 18, at 5.

[264] Deuterium kinetic isotope effects are expressed as a ratio of the rate of C–H bond cleavage over the rate of C–D bond cleavage, k_H/k_D. *See* Wade, *supra* note 28, at 193. *See also supra* notes 28-33 and accompanying text.

[265] Metabolism typically results in deactivation of the drug, and consequently produces undesired molecules which can exhibit varying activities. *See* Foster, *supra* note 18, at 2.

[266] *See* Foster, *supra* note 18, at 4. There are many metabolic pathways implicated in pharmacokinetics, some of which involve C–H bond cleavage and are thus amenable to deuterium substitution. *See* THOMAS, *supra* note 256, at 446. Examples of C–H metabolism include arene oxidation, and oxidation of alkyl and benzylic sites. THOMAS, *supra* note 256 at 446-47. Examples of metabolism which do not break C–H bonds are the oxidation of heteroatoms such as sulfur or nitrogen to sulfoxides, sulfones, or *N*-oxides, or the hydrolysis of esters and amides. THOMAS, *supra* note 256 at 446-48.

[267] CoNCERT Pharmaceuticals, Inc. in Lexington, MA and Auspex Pharmaceuticals in Vista, CA have drug development programs targeting deuterated small molecules with improved safety and efficacy over their

NCEs, are not only a means of gaining entry into well-defined therapeutic areas. They also represent an opportunity to improve the metabolic profile of existing drugs.[268]

Whether the deuterated analogs of prior art compounds are obvious over their protio versions has not yet been addressed by any court. However, litigation is almost a certainty because of the expected competition between the deuterated and protio forms.[269] Most pharmaceutical companies invest a great deal of

protio versions. For example, CoNCERT Pharmaceuticals has been issued patents for deuterated versions of rimonabant (U.S. Patent No. 7,541,068 (filed Sept. 14, 2006)) and mosapride (U.S. Patent No. 7,528,131 (filed Apr. 18, 2008)). CoNCERT has applied for patents covering deuterated versions of the antidepressants Wellbutrin® (U.S. Patent Application No. PCT/US09/01040 (filed Feb. 19, 2009)), Paxil® (U.S. Patent Application No. 11/498,334 (filed July 31, 2006)), the Hepatitis C virus (HCV) protease inhibitor boceprevir (U.S. Patent Application No. PCT/US08/12949 (filed Nov. 20, 2008)), and the erectile dysfunction drug Cialis® (U.S. Patent Application No. 11/704,555 (filed Feb. 8, 2007)). Auspex Pharmaceuticals has obtained a patent on a deuterated version of the antidepressant Effexor® (U.S. Pat. No. 7,456,317 (filed Nov. 30, 2006)), and has filed applications covering deuterated versions of the fungicidal drug Lamisil® (U.S. Patent Application No. 11/953,195 (filed Dec. 10, 2007)) and the antibiotic Zyvox® (U.S. Patent Application No. 11/949,402 (filed Dec. 3, 2007)). *See* www.concertpharma.com and www.auspexpharma.com for further information. Additionally, an intellectual property holding company, Protia, L.L.C. located in Reno, Nevada, has applied for patents covering deuterated analogs of well-known drugs such as Singulair® (U.S. Patent Application No. 11/766,140 (filed June 21, 2007)), Plavix® (U.S. Patent Application No. 11/765,434 (filed June 19, 2007)), Lipitor® (U.S. Patent Application No. 11/745,704 (filed May 8, 2007)), and Lunesta® (U.S. Patent Application No. 11/765,435 (filed June 19, 2007)). *See* www.protia.com for additional information.

[268] *See* CoNCERT Pharmaceuticals, Inc., Precision Deuterium Chemistry Backgrounder (2007), http://www.concertpharma.com, *archived at* http://www.webcitation.org/5e81SGCnl (stating that deuterated analogs exhibit improved safety profiles through a reduction in the formation of toxic metabolites, better tolerability through a reduction of overall dose, and enhanced efficacy through an increase in bioavailability); Auspex Pharmaceuticals Brochure, 2009 http://www.auspexpharma.com/About_Us.html, *archived at* http://www.webcitation.org/5e812nnON (stating that Auspex Pharmaceuticals can rapidly generate potential best-in-class therapeutics while reducing the time, cost, and risk of drug development).

[269] *See* Furrow, *supra* note 1, at 277 (arguing that the "loose nature" of nonobviousness jurisprudence invites challenges to "evergreening" patents by asserting that the patents were actually obvious). "Evergreening" is a strategy

money and time developing a new therapeutic drug.[270] The incentive to spend millions on drug development is rewarded upon FDA approval with market exclusivity.[271] The generic market erodes this profitable exclusivity within a relatively short time after FDA-approval.[272] Deuterated competition will further

whereby patentees attempt to prolong the effective market life of a pharmaceutical by filing for "secondary" or "follow-on" patents. *Id*. Follow-on discoveries usually result from late-stage drug development efforts, but may include the patenting of single enantiomers or new salt forms or formulations. *Id*. *See also* O'Driscoll, *supra* note 40, at 26 (asserting that any litigation will be lengthy if the deuterated drugs demonstrate a real advantage) (citing Alan Johnson of the London law firm Bristows). The stakes may be higher than mere competition with the protio brand, as drugs already approved by the FDA may ultimately pave the way for expedited approval of their deuterated counterparts, thereby streamlining the clinical testing of such agents and reducing the overall cost of bringing the drugs to market. Yarnell, *supra* note 45, at 39. Regardless, CoNCERT's strategy most definitely reduces the risk of failure during drug development as the clinical profiles of the protio versions are established prior to any clinical trial involving its deuterated counterpart. Yarnell, *supra* note 45, at 39.

[270] *See* Furrow, *supra* note 1, at 283 (stating that the development time of an FDA-approved drug averages between ten to fifteen years at a cost of $1.5 billion per drug).

[271] *But see* Matthew Avery, Note, *Continuing Abuse of the Hatch-Waxman Act by Pharmaceutical Patent Holders and the Failure of the 2003 Amendment*, 60 HASTINGS L.J. 171, 172 (stating that only three of every ten marketed drugs are commercially successful enough for the patentee to recoup its research and development costs).

[272] *See* Hatch-Waxman Act, 21 U.S.C. § 355(j) (2009) and 35 U.S.C. §§ 156, 271(e) (2009). The Hatch-Waxman Act facilitates generic competition by requiring a generic manufacturer to demonstrate only that the generic drug has the same active ingredient, the same basic pharmacokinetics, and is bioequivalent to the parent drug. Avery, *supra* note 271, at 176. The Hatch-Waxman Act eliminates the need for generic companies to provide independent proof of safety and efficacy, which substantially increases the expense associated with generic drug manufacturing. Avery, *supra* note 271, at 176. The Hatch-Waxman Act thus attempts to balance the conflicting policy objectives of encouraging investment in the research and development of new drug therapies while enabling generic competitors to market cheaper versions of the parent drugs. Avery, *supra* note 271, at 175. Under the Hatch-Waxman Act, a company wishing to market a generic version of a patented product must certify: (I) that the parent drug is not patented; (II) that its patent has expired; (III) that the generic product will not go on the market until the patent expires; or (IV) that the patent is invalid or will not be infringed by the generic manufacturer. Avery, *supra* note 271, at 176. A generic manufacturer who makes a paragraph IV certification must notify the patent owner of a legal

reduce the market for the parent drug, potentially even rendering the protio version obsolete if the differences between the deuterated and protio compounds are significant.

Traditionally, pharmaceutical patents disclosed hydrogen as one of the many substituents one might incorporate into a therapeutic drug but did not specifically identify deuterium as a suitable alternative to hydrogen.[273] However, the landscape of pharmaceutical patents has changed markedly in the last several years as the technical strategies of CoNCERT Pharmaceuticals and Auspex Pharmaceuticals became known through the publication of their patent applications. While once infrequently mentioned in the context of a composition of matter patent of a therapeutic agent, deuterium is now routinely cited in the specification for its presumed effects on metabolic stability.[274] The disclosure of deuterium in the specification without claiming specific deuterated compounds has further implications on the validity analysis of a later claimed isotopolog.[275] However, the

justification for the invalidity of the patent. Avery, *supra* note 271, at 177. A Paragraph IV certification is itself an act of patent infringement, and usually results in an infringement lawsuit brought by the patent holder. Avery, *supra* note 271, at 177.

[273] *See, e.g.,* U.S. Patent No. 4,535,186 (filed Oct. 26, 1983) (issued Oct. 12, 1982) (claiming Effexor®); U.S. Patent No. 4,681,893 (filed May 30, 1986) (issued July 21, 1987) (claiming Lipitor®); U.S. Patent No. 4,007,196 (filed July 23, 1975) (issued Feb. 8, 1977) (claiming Paxil®); U.S. Patent No. 4,018,895 (filed Sept. 17, 1975) (issued Apr. 19, 1977) (claiming Strattera®).

[274] *See, e.g.,* U.S. Patent Application No. 12/065,923 (filed Sept. 7, 2006) (assigned to GlaxoSmithKline), U.S. Patent Application No. 12/067,885 (filed Sept. 27, 2006) (assigned to Boehringer Ingelheim), U.S. Patent Application No. 11/772,995 (filed July 3, 2007) (assigned to Pfizer), U.S. Patent Application No. 11/917,355 (filed June 13, 2006) (assigned to SmithKline Beecham), U.S. Patent Application No. 11/995,888 (filed July 27, 2006) (assigned to Johnson & Johnson), and U.S. Patent Application No. 12/002,883 (filed Dec. 19, 2007) (assigned to Millennium Pharmaceuticals). Representative language reads, in part, "substitution with isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances." U.S. Patent Application No. 11/570,564 (filed Oct. 6, 2006).

[275] Although disclosed, the isotopolog genus may not be enabled by the specification because the synthetic routes to deuterated compounds may differ substantially from the synthetic routes to the parent compounds. *See* Sanofi-Synthelabo, Inc. v. Apotex, Inc, 550 F.3d 1075, 1085 (Fed. Cir. 2008). Thus, the patentee would have to describe the synthetic route to the

genus of a deuterated analog is inherently disclosed in the parent molecule because the parent necessarily suggests the possible isotopologs that can be synthesized.[276] Therefore, whether an isotopolog is obvious in light of its prior art genus can be addressed through the law of obviousness as applied to other genus-species relationships in the chemical arts, as outlined above.

As the court stated in *Dillon*, the obviousness of a deuterated prior art compound is premised on the inventor's motivation and expectation of success in modifying the compound, which together establish a prima facie case of obviousness.[277] Many of the isotopologs currently claimed in patent applications are derived from drugs that have either been approved by the FDA or are undergoing clinical trials.[278] For this reason, these parent molecules have desirable properties that make them worthy of investment.[279] Thus, the scientists will most likely be shown to have had the requisite motivation to alter prior art structures in an effort to achieve a cleaner metabolic profile.

However, a prima facie case of obviousness is not established when the genus encompassing a claimed species is so large that one of ordinary skill in the art would not have a reasonable expectation of success in selecting that species from

isotopolog specifically and not by general reference to the parent synthetic route to enable the isotopolog. *Id.* at 1085 (stating that despite a presumption of enablement for an issued patent, a person of ordinary skill in the art must be able to practice the invention as disclosed without undue experimentation). Further, the disclosed genus may not be anticipatory under 35 U.S.C. § 102 (2006) because the genus does not disclose the claim limitations of a specific isotopolog. *Id*. at 1083 (stating that an anticipating reference must specifically describe and enable the subject matter at issue).

[276] An isotopolog genus is inherent in the parent molecule from which it is derived because every hydrogen on the parent can be substituted with deuterium to produce a species within the genus; thus, the parent structure suggests all possible deuterated analogs. *Sanofi*, 550 F.3d at 1081.

[277] *See In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc).

[278] *See* CoNCERT Pharmaceuticals, Inc., Precision Deuterium Chemistry Backgrounder (2007), http://www.concertpharma.com, *archived at* http://www.webcitation.org/5e81SGCnl (stating that CoNCERT's product platform is derived from existing, validated drugs).

[279] *See supra* note 267 for representative examples of FDA-approved drugs.

amongst other members of the genus. Because the genus of a single enantiomer contains only two species, an enantiomer must exhibit substantially different characteristics than its racemate to survive an obviousness challenge.[280] Conversely, the use of Markush groups in patents claiming chemical compositions of matter allows for the description of a large genus of structurally similar molecules. The larger the genus, the less likely an inventor will be shown to have possessed the requisite reasonable expectation of success sufficient to support a prima facie case of obviousness.[281] Thus, a species within a larger disclosed genus of analogs may be nonobvious before consideration of any evidence of unexpected results.[282] However, a smaller genus which encompasses bioisosters or homologs may render the later claimed species obvious when the individual species do not demonstrate markedly different properties from other members of the genus.[283]

The genus of salt forms consists essentially of the FDA-approved salts referred to by the *Pfizer* court.[284] This genus contains fifty-three species, and thus is relatively small. Because of the finite size of this genus, a novel salt form must exhibit substantially different and unexpected properties relative to the other members of the genus.[285] Similarly, the genus of formulation techniques is limited in number and generally

[280] Sanofi-Synthelabo, Inc. v. Apotex, Inc, 550 F.3d 1075, 1089 (Fed. Cir. 2008); *In re* May, 574 F.2d 1082, 1095 (C.C.P.A. 1978). However, the challenges associated with the separation of enantiomers will often render the single enantiomer nonobvious. *See* Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007).

[281] *Takeda*, 492 F.3d at 1357 (holding that a genus of "hundreds of millions of TZD compounds" did not suggest to one of ordinary skill in the art the claimed compound).

[282] *Id*. at 1354, 1363. *See also* Wegner, *supra* note 62, at 440 (reasoning that even a slight modification in structure may fundamentally change the physiological interaction between the biological receptor and a drug, thereby establishing evidence of unexpected results).

[283] *In re* Hass, 141 F.2d 122, 125 (C.C.P.A. 1944); *In re* Merck, 800 F.2d 1091, 1099 (Fed. Cir. 1986) (stating that an inability to provide evidence of actual differences between a prior art structure and its bioisostere supports a finding of obviousness).

[284] *See* Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1371 (Fed. Cir. 2007).

[285] *Id*. Evidence of beneficial properties which merely facilitate the commercial manufacturing and marketing of a pharmaceutical product may not be sufficient to rebut a prima facie case of obviousness. *Id*.

known throughout the industry. Accordingly, a new formulation of a prior art compound must demonstrate unexpected characteristics not possessed by other formulations to be nonobvious.[286]

The genus of deuterated compounds is also finite because the parent molecules from which they are derived have a finite number of hydrogens which can be substituted with deuterium. For example, the chemical structure of Cymbalta® contains twenty-one hydrogen atoms which may be substituted for deuterium. Of these hydrogens, one is readily exchanged under aqueous conditions and thus is not a productive site for deuterium substitution.[287] Further, several hydrogens on Cymbalta® are chemically equivalent and for practical reasons would most likely be substituted together or not at all.[288] After accounting for these hydrogen atoms, Cymbalta® contains fifteen non-equivalent and non-exchangeable hydrogens which may be substituted by deuterium, resulting in 32,767 possible combinations of deuterium substitution.[289] Further, this number

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[286] *See* Bayer Schering Pharma A.G. v. Barr Labs. Inc., No. 05-cv-2308, 2008 WL 628592, at *24 (D.N.J. Mar. 3, 2008), *aff'd*, 575 F.3d 1341 (Fed. Cir. 2009).

[287] Chemically exchangeable hydrogens are those which are capable of being transferred from one molecule to another. BRUICE, *supra* note 110, at G-3. For example, exchangeable hydrogens are most often located on nitrogen (N) and oxygen (O) atoms and undergo exchange between that atom and water. BRUICE, *supra* note 110, at G-3.

[288] Chemically equivalent hydrogens are those which have the same connectivity relationship to the rest of the molecule. BRUICE, *supra* note 110, at G-3. For example, the hydrogens on a methyl group (CH_3) are all chemically equivalent. BRUICE, *supra* note 110, at G-3.

[289] The number of possible deuterated compounds in Cymbalta's® genus is calculated using the sum of the binomial coefficients for each of the deuterated sites: $\sum_{k=1}^{k=n} \frac{n!}{k!(n-k)!}$, where n = the number of chemically non-equivalent hydrogens on the molecule and k = the number of deuterated sites for any given combination, from mono-deuterated to per-deuterated. This equation simplifies to $\sum_{k=1}^{k=n} \frac{n!}{k!(n-k)!} = 2^n - 1$ for all possible combinations of n chemically non-equivalent hydrogens. *See* Paulo Provero, Combinatorics (2007), http://personalpages.to.infn.it/~provero/master_2007/combinatorics.pdf,

would be expected to be higher when chemically equivalent hydrogens are differentially substituted, giving rise to stereoisomers or other analogs.[290]

The seemingly large genus which encompasses an isotopolog would seem to support a finding of nonobviousness, because one of ordinary skill in the art would lack an expectation of success in selecting a specific compound from among other members of the genus.[291] Applying the court's reasoning in *Takeda*, a person of ordinary skill in the art would have to have a reasonable expectation of success in selecting a deuterated compound from the thousands of potential molecules within the genus to support a prima facie case of obviousness.[292] However, a challenger may establish an expectation of success with evidence that the metabolism of the parent compound was extensively profiled and resulted in public knowledge of the drug's pharmacokinetics.[293] Because the knowledge of actual metabolites can help guide the selection of promising sites of deuteration, the compounds may not be chosen at random from

archived at http://www.webcitation.org/5edLAv98K. For example, all possible combinations of deuteration on Cymbalta® are calculated as $2^{15} - 1 = 32{,}767$. Strattera® contains thirteen non-equivalent, non-exchangeable hydrogens whose genus contains 8,191 members. Paxil® contains twelve non-equivalent, non-exchangeable hydrogens and is a member of a genus whose size is 4,095. Cialis® also contains thirteen non-equivalent, non-exchangeable hydrogens and is a member of a genus encompassing 8,191 species.

[290] The possible combinations of deuterated compounds for any given molecule calculated by $2^n - 1$ would therefore be a lower limit for the number of species within a defined genus. If all possible combinations of deuterium incorporation were contemplated without consideration of chemical equivalence, the genus of isotopologs derived from Cymbalta® would be $2^{20} - 1 = 1{,}048{,}575$.

[291] *See* Takeda Chem. Indus. v. Alphapharm Pty. Ltd., 492 F.3d 1350, 1360 (Fed. Cir. 2007).

[292] *Id*. at 1357.

[293] *See* CoNCERT Pharmaceuticals, Inc., Precision Deuterium Chemistry Backgrounder 18 (2007), http://www.concertpharma.com, *archived at* http://www.webcitation.org/5e81SGCnl (stating that CoNCERT's compounds are based on drugs with known efficacy and safety profiles). However, a reasonable expectation of success may not be established if the owner of the parent compound has not published or otherwise made available the pharmacokinetic profile of the drug. *Id*.

the thousands of possibilities within the genus.[294] Therefore, any challenger will probably be able to establish a prima facie case of obviousness, because there is substantial motivation and an expectation of success in deuterating prior art drugs with known metabolic profiles.[295]

Even if a prima facie case of obviousness is established based on structural similarity and an expectation of success, evidence of unexpected results that the isotopolog is actually different from its protio version substantiates a finding of nonobviousness.[296] Evidence of unexpected results can be demonstrated by examples in which deuteration was unsuccessful despite knowledge that metabolism at that site is primarily responsible for degradation of the protio drug in vivo.[299] There exists the possibility that some may be more effective than others in attenuating metabolism because there are many sites on the molecule that may be deuterated.[297]

An example of unexpected results following the deuteration of a prior art compound is shown in CoNCERT's case study on torcetrapib.[298] Based on the available metabolic data,

[294] Further, the possible sites of deuteration are finite in number because there are a finite number of hydrogens on the parent molecule. Therefore, there are a finite number of combinations which would, in theory, eventually lead to a successful candidate.

[295] *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc). *See also* Spenner, *supra* note 3, at 478 (stating that *KSR* reaffirms the "finite" obvious-to-try rationale to support a prima facie case of obviousness when there are a finite number of possible solutions).

[296] *Takeda*, 492 F.3d at 1364 (Dyk, J., concurring) (reasoning that a claimed species within a prior art genus may be patentable only if the species exhibits unexpected results).

[299] Examples of unsuccessful deuteration may be characterized by no decrease in the observed rate of metabolism and may suggest that metabolic switching or shunting has occurred. Foster, *supra* note 18, at 6.

[297] *See* CoNCERT Pharmaceuticals, Inc., Precision Deuterium Chemistry Backgrounder (2007), http://www.concertpharma.com, *archived at* http://www.webcitation.org/5e81SGCnl (stating that the magnitude and nature of the deuterium benefit cannot be predicted a priori).

[298] *See id.* Torcetrapib was created by Pfizer to raise HDL cholesterol, but development was halted when undesirable side effects were observed in Phase III clinical trials. *See* Derek Lowe, *The Torcetrapib Catastrophe*, Dec. 3, 2006,

scientists at CoNCERT identified twelve different deuterated analogs that were likely to inhibit undesired metabolism.[299] Of the twelve, six showed surprising metabolic stability whereas the other six showed metabolic profiles comparable to torcetrapib.[300] This small series of deuterated analogs rapidly identified the most significant site of oxidative metabolism on the molecule, which was unexpected and could not have been predicted.[301] This experiment therefore illustrates that even armed with the metabolic profiles of successful drugs, it is still not possible to predict which compounds will succeed and which will fail.

X. Conclusion

The statutory requirement of nonobviousness is the most nebulous requirement in patent law. Obviousness as applied to the chemical and pharmaceutical arts is even more difficult to assess due to the fundamental unpredictability associated with these fields. Thus, despite a seemingly low barrier for establishing a prima facie case of obviousness, chemical compounds are often rendered nonobvious because of unexpected differences between the claimed structures and the prior art. Although the obviousness of deuterated compounds has not yet been addressed, it is clear from the case law that the deuterated analogs will most likely be obvious absent evidence of actual and unexpected differences between the prior art and the deuterated compounds. Therefore, whether deuterated analogs are obvious over prior art compounds ultimately depends on how differentiated the deuterated compounds are from their protio versions.

http://pipeline.corante.com/archives/2006/12/03/the_torcetrapib_catastrophe.php, *archived at* http://www.webcitation.org/5e9b6IMGz.

[299] *See* CoNCERT Pharmaceuticals, Inc., Precision Deuterium Chemistry Backgrounder (2007), http://www.concertpharma.com, *archived at* http://www.webcitation.org/5e81SGCnl.

[300] *Id*.

[301] *Id*.