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THE VALIDITY CHALLENGE TO COMPOUND CLAIMS AND THE (UN?)PREDICTABILITY OF CHEMICAL ARTS

Guyan Liang, Ph.D., J.D.[†]

[†] Associate, Budd Larner, P.C.; Advisory board member, Center for Drug Design, Mercer University College of Pharmacy and Health Sciences. Prior to his legal career, the author worked as a research scientist in drug discovery for fifteen years. The views expressed herein are the personal views of the author and do not necessarily reflect those of Budd Larner or any other organizations with which the author was affiliated. The author would like to thank Mr. Andrew Miller for his support. The author also would like to acknowledge Professor Jordan Paradise for her critical review of the manuscript and insightful comments.

I. INTRODUCTION

Pharmaceutical research and development ("R&D") is a lengthy and expensive endeavor with a possibility of high return, yet a low probability of success. In 2006, 105 drugs had annual sales of more than one billion US dollars, and the best-selling drug, Lipitor® from Pfizer, topped off at nearly $14 billion.[1] Developing a drug, however, takes from ten to fifteen years with an average cost around $1.3 billion.[2] For every 5,000 to 10,000 compounds investigated in medicinal chemistry, about 250 may progress into preclinical evaluation, five of which may enter clinical studies, and one lucky compound may eventually receive approval for marketing from the United States Food and Drug Administration (the "FDA").[3]

Whether pharmaceutical companies that invest in drug discovery can recover their investment depends heavily on the patent protection of their drugs. If the patent expires or is declared invalid, the price of a drug decreases significantly under generic competition.[4] The validity of those patent claims, especially compound claims, often is the subject of fierce litigation, the resolution of which may impact billions of dollars of business revenue. Often, the validity challenge to a compound claim is based on the theory that the claimed invention was obvious in light of the prior art available at the time of the invention to a person having ordinary skill in the art. While the general principle of obviousness analysis applies to chemical compound claims, the courts have also developed a special analysis for chemical compound cases because of the perceived unpredictability of the chemical art.[5] However, as will be discussed in this article, this assumption may not always be true and should not be treated as it is.

Part II of this article will discuss the Hatch-Waxman Act, which

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[1] Andrew Humphreys, *Med Ad News 200 world's best-selling medicines*, MED AD NEWS (July 1, 2007), *available at* http://business.highbeam.com/437048/article-1G1-167388387/med-ad-news-200-world-bestselling-medicines-lipitor.

[2] *Pharmaceutical Industry Profile 2011*, PHARM. RES. & MFRS. OF AM., 10, 12 (April 2011), *available at* http://www.phrma.org/sites/default/files/159/phrma_profile_2011_final.pdf.

[3] *Id.*

[4] Frank R. Lichtenberg & Gautier Duflos, *Time release: The Effect of Patent Expiration on U.S. Drug Prices, Marketing, and Utilization by the Public*, MANHATTAN INST. FOR POL'Y RES. (October 2009), http://www.manhattan-institute.org/html/mpr_11.htm (stating that between twelve and sixteen years after launching, the average generics' mean market share increases from eight percent to sixty-five percent while the mean price declines forty-four percent).

[5] *See In re* Dillon, 919 F.2d 688, 698 (Fed. Cir. 1990).

was introduced in 1984 and created the generic drug pathway to the market. Within this framework, the validity of drug patents are often challenged based on various theories including that the claimed invention was obvious to a person skilled in the art. Part III will discuss the general legal principle of the obviousness analysis under the context of patent validity, including the impact of *KSR v. Teleflex* ("*KSR*").[6] Part IV will discuss the evolution of obviousness analysis for chemical compound claims, leading toward the development of the modern lead compound theory. Part V will survey applications of the lead compound theory in the Court of Appeals for the Federal Circuit (the "CAFC") since 2006 and discuss the teachings of each case. As will be discussed in more detail, the lead compound theory and those decisions applying the lead compound theory are largely based on the presumption that properties of chemical arts are unpredictable and that a small change in chemical structure may cause a significant variation in properties. Therefore, according to the CAFC, structural similarity alone does not suffice to establish a prima facie case of obviousness. As will be discussed in Part VI, however, this is not always true. Many strategies and approaches used in modern drug discovery, such as structure activity relationship ("SAR") analysis in medicinal chemistry and rational drug design, can be used to predict properties of chemical compounds. It should be recognized by the courts that properties of chemical arts are not always unpredictable and that a properly validated prediction can contribute to the obviousness analysis in patent validity litigation.

II. HATCH-WAXMAN ACT AND GENERIC DRUGS

The pharmaceutical industry is a heavily regulated industry, and a new drug cannot be marketed in this country without approval by the FDA.[7] If the innovator company believes that its newly-discovered compound can be used to treat certain diseases, it may sponsor clinical trials of the drug by filing an Investigational New Drug Application ("IND") with the FDA, which includes a summary of animal pharmacology and toxicity studies, chemistry and manufacturing information, and proposed clinical protocols.[8] If the FDA does not object to the IND within thirty days, the innovator company may start

[6] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398 (2007).

[7] *See* 21 U.S.C. § 321 (2006); *see also* Patricia I. Carter, *Federal Regulation of Pharmaceuticals in the United States and Canada*, 21 LOY. L.A. INT'L & COMP. L.J. 215, 229 (May 1999).

[8] *See* Carter, *supra* note 7, at 231.

the clinical trials outlined in the IND.[9] After all clinical trials have been completed and all data have been analyzed, the innovator company may file a New Drug Application ("NDA"), outlining the route of administration, dosage, intended use, labeling, etc.[10] Once the FDA approves the NDA, the innovator company may market the new drug in the United States.[11]

The innovator company, having invested heavily in the preclinical research, clinical trials, and approval process of the new drug, is entitled to an exclusive marketing right that is guaranteed by both patent law and the FDA data exclusivity provision, whichever is longer.[12] As a patent holder, the innovator company has a right to exclude others from practicing the patented invention in the United States within the term of the patent, which is seventeen years from the date of issuance for patents filed on or before June 8, 1995, or twenty years from the date of filing for patents filed after that date.[13] A patent term extension is available to compensate the patent holder for delays in the patent review and FDA approval processes if the patent holder acted with due diligence during the period.[14] Parallel to the patent protection, the innovator company is also entitled to a five-year period of data exclusivity from the date of FDA approval if the new drug product contains a New Chemical Entity ("NCE") never previously approved by the FDA alone or in combination with other chemical entities.[15] Within the period of the data exclusivity, no generic drug application can be filed with the FDA unless accompanied by a paragraph IV certification.[16]

Paragraph IV is a provision in the Drug Price Competition and Patent Term Restoration Act, passed by Congress in 1984 to encourage competition.[17] The Act was jointly sponsored by Senator Orrin Hatch and Representative Henry Waxman, and thus is commonly referred to as the Hatch-Waxman Act.[18] The Hatch-

[9] *Id.* at 231.

[10] *See* 21 U.S.C. § 355(b) (2006); *see also* 21 C.F.R. §§ 56, 314 (2012).

[11] *See* 21 U.S.C. § 355(a) (2006).

[12] *See* 21 U.S.C. § 355(j)(5)(F)(ii) (2006).

[13] *See* 35 U.S.C. § 154(a)(2) (2006).

[14] *See* 35 U.S.C. § 156 (2006).

[15] *See* 21 U.S.C. § 355(j)(5)(F)(ii) (2006).

[16] *Id.*

[17] Drug Price Competition and Patent Restoration Act of 1984, Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1586 (1984) (codified in 21 U.S.C. § 355).

[18] *See* Ronald Reagan, President of the U.S., Remarks on Signing the Drug Price Competition and Patent Term Restoration Act of 1984, Speech in the Rose Garden at the White House (Sept. 24, 1984), *in* 1984 Book II PUB. PAPERS 1362 (published 1987).

Waxman Act allows generic manufacturers to gain FDA marketing approval by filing an Abbreviated New Drug Application ("ANDA") if they can demonstrate that the proposed generic drug and the original NDA drug are bioequivalent.[19] To reduce market entry delays for generic drugs, the Hatch-Waxman Act has a safe harbor provision that exempts otherwise infringing activities that are solely and reasonably related to obtaining FDA approval for a drug.[20] To file an ANDA, the generic manufacturer must provide one of the following paragraph certifications: (I) that no patent information on that brand name drug has been submitted to the FDA; (II) that the listed patent has expired; (III) that the listed patent will expire on a certain date, before which time the generic will not enter the market; or (IV) that the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the ANDA was submitted.[21] If a generic manufacturer submits a paragraph IV certification, the five-year data exclusivity period for the original NDA sponsor is reduced to four years, which allows the FDA to accept and review the ANDA filing one year before the expiration of the original data exclusivity period.[22] Additionally, the earliest ANDA filer who prevails in the infringement litigation receives 180 days of market exclusivity for the generic drug, creating a strong financial incentive for ANDA filings with a paragraph IV certification.[23] While paragraph I to III certifications are relatively straightforward, the paragraph IV certification is not so simple.

The generic manufacturer that files a paragraph IV certification for its ANDA must notify the patent holder of the original NDA drug of its paragraph IV certification submission and provide a detailed legal and factual explanation to substantiate that its proposed generic drug does not infringe the relevant patent or that the patent is invalid.[24] The mere filing of the paragraph IV certification is an act of infringement, based on which the original patent holder has forty-five days to file an infringement suit.[25] If the patent holder does not file an infringement suit within forty-five days, the FDA can approve the ANDA

[19] *See* 21 U.S.C. § 355(j) (2006). (In general, the generic drug is defined as bioequivalent to the original NDA drug if its blood concentration deviates less than 20% from the NDA drug. Upon finding of bioequivalence, the ANDA can rely on the corresponding NDA's finding of safety and efficacy without additional clinical trials).

[20] *See* 35 U.S.C. § 271(e)(2)(A), (e)(5) (2006).

[21] *See* 21 U.S.C. §§ 355(b)(2)(A)(i)-(iv) (2006).

[22] *See* 21 U.S.C. § 355(c)(3)(E)(ii) (2006).

[23] *See* 21 U.S.C. § 355(j)(5)(B)(IV)(iv)(I) (2006).

[24] *See* 21 U.S.C. § 355(b)(3)(D)(ii) (2006).

[25] 21 U.S.C. § 355(c)(3)(C) (2006).

immediately.[26] However, if an infringement suit is filed, the FDA may not approve the ANDA within thirty months or until a court rules that the patent is invalid or not infringed, whichever is earlier.[27]

The most typical and often-used defense to this kind of infringement suit is that the original patent is invalid because the relevant claim or claims were obvious to a person having ordinary skill in the art ("PHOSITA" or "skilled artisan") in light of the prior art available at the time of the invention. This process is applicable to all patents cited for NDA drugs in the Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") published by the FDA.[28] In order to assert their patent rights in FDA filings and related judicial proceedings, NDA filers must list in the Orange Book all patents relevant to each NDA drug, which includes dosage patents, salt patents, formulation patents, and, most importantly, compound patents, which are the focus of the present article. Before going into specific analysis of compound patents in section IV, the next section will discuss the general legal principles of obviousness analysis in the context of patent validity.

III. THE GENERAL PRINCIPLE OF OBVIOUSNESS ANALYSIS

Pursuant to Title 35 of the United States Code, to be patentable an invention must be useful,[29] novel,[30] non-obvious,[31] and described in sufficient detail to enable its use by one skilled in the art.[32] Articulated in 35 U.S.C. § 103, the non-obviousness requirement prevents patenting when "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."[33] In determining the non-obviousness of an invention, the Supreme Court, in *Graham v. John Deere Co.*, enumerated three factors to be considered, including (1) the scope and

[26] *Id.*

[27] 21 U.S.C. § 355(c)(3)(C)(i) (2006).

[28] U.S. Dep't of Health & Human Servs., Food & Drug Admin., Ctr. for Drug Evaluation & Research, Office of Pharm. Sci., Office of Generic Drugs, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations (32d ed. 2012), *available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[29] 35 U.S.C § 101 (2011).

[30] 35 U.S.C § 102 (2011).

[31] 35 U.S.C § 103 (2011).

[32] 35 U.S.C § 112 (2011).

[33] 35 U.S.C § 103 (2011).

content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the art.[34] "As indicia of obviousness or nonobviousness," some secondary factors, such as "commercial success, long-felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."[35] The *Graham* factors laid a foundation and provided a general guideline for obviousness analysis of an invention in light of the prior art.

To determine whether an invention derived from a combination of previously known elements is obvious in light of the prior art, the CAFC in *Winner Int'l Royalty Corp. v. Wang* introduced the teaching-suggestion-motivation ("TSM") test.[36] In that case, both Winner and Wang owned patents claiming embodiments of anti-theft car immobilization devices commercially known as "The Super Club" and "The Gorilla Grip."[37] While various features and elements of those devices were known in the prior art, one central dispute was whether the combination of those previously known elements was obvious to a person having ordinary skill in the art at the time of the invention. Applying the *Graham* factors to the case, the CAFC panel held that to find a patent obvious there must be something in the prior art to suggest, teach, or motivate the combination of the previously known elements, thus, the TSM test.[38] Evidence of a teaching, suggestion, or motivation to combine the prior art references, according to the CAFC, can be found from the references themselves, the knowledge of the ordinarily skilled artisan, or from the nature of the problem to be solved.[39] Moreover, although the prior art reference does not have to teach or explicitly suggest the combination of the previously known elements, the showing of combinability must be clear and particular.[40] In *Winner*, no evidence of a teaching, suggestion, or motivation to combine the previously known elements was found, thus the claimed

[34] Graham v. John Deere Co., 383 U.S. 1, 17 (1966) ("While the ultimate question of patent validity is one of law . . . the § 103 condition, which is but one of three conditions, each of which must be satisfied, lends itself to several basic factual inquiries. Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.").

[35] *Id.* at 17–18.

[36] Winner Int'l Royalty Corp. v. Wang, 202 F.3d. 1340, 1348 (Fed. Cir. 2000).

[37] *Id.* at 1342–43.

[38] *Id.* at 1348.

[39] *Id.*

[40] *Id.* at 1348–49.

invention was not obvious to a skilled artisan at the time of the invention.[41]

While the TSM test serves the purpose of preventing hindsight bias, it has been criticized as being too rigid, which was addressed by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*[42] In that case, Teleflex asserted that KSR infringed on Teleflex's patent of connecting an adjustable vehicle control pedal to an electronic throttle control.[43] In its defense, KSR argued that both elements (adjustable vehicle control pedal and electronic throttle control) were known in the prior art and that combining those elements was obvious to a person having ordinary skill in the art at the time of the invention.[44] While the District Court ruled in KSR's favor, the CAFC reversed, reasoning that the District Court did not strictly apply the TSM test.[45] The Supreme Court disagreed with the CAFC on how the TSM test should be applied.[46] In its unanimous opinion, the Supreme Court stated that "[t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents."[47] As noted by the Supreme Court, the question is not whether the combination was obvious to the patentee but rather to a person having ordinary skill in the art at the time of the invention.[48] Additionally, the element being combined does not need to come from the same field or be designed to solve the same problem.[49] As stated by the court, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton."[50]

In the *KSR* opinion, the Supreme Court noted and encouraged the new trend in subsequent CAFC decisions that "elaborated a broader conception of the TSM test."[51] While *KSR* did not overrule the TSM test, it lowered the bar for the TSM test and made it easier in general to challenge the validity of a patent based on obviousness. For chemical compound patents, however, the impact of *KSR* is limited so

[41] *Id.* at 1350.
[42] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398 (2007).
[43] *Id.* at 406.
[44] *See id.* at 399.
[45] *Id.* at 400.
[46] *Id.* at 419.
[47] *Id*.
[48] *Id.* at 420.
[49] *See id.* at 420–21.
[50] *Id.* at 421.
[51] *Id.* at 421–22.

far.

IV. THE DEVELOPMENT OF THE LEAD COMPOUND THEORY

The obviousness analysis for chemical compounds has gone through several stages, focusing mainly on the issue of whether teachings beyond structural similarity are required for a prima facie case of obviousness. Established in 1950 and governing the field for twenty years, the Hass-Henze doctrine maintained that structural similarity alone was adequate to establish a prima facie case of obviousness for chemical compound cases.[52] Overruling the Hass-Henze doctrine in 1971, the *In re Stemniski* court demanded a showing or teaching in the prior art beyond structural similarity.[53] This view controlled the field for another twenty years and occasionally led to extreme results. In 1990 the CAFC issued a milestone *en banc* decision, *In re Dillon,* clarifying the prior confusion and setting forth a revised analysis that remains in use today. *In re Dillon* did not directly cite, but adhered to, the same principle as the TSM test.[54] In 2000, the Y*amanouchi* court further developed the principle into a two-step process, thus formalizing what is now known as the lead compound theory.[55]

A. The Hass-Henze Doctrine

The Hass-Henze doctrine, established by *In re Hass*[56] and *In re Henze*[57] and later overruled by *In re Stemniski*,[58] was an early attempt by the United States Court of Customs and Patent Appeals (the "CCPA"), the predecessor of the CAFC, to analyze the obviousness of chemical arts for the purposes of patentability and validity. The doctrine, which predated the *Graham* Factors and the TSM test, was predicated on the court's belief that chemical compounds of a homologous series shared similar chemical and physical properties which varied only gradually from member to member.[59]

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[52] Gregory L. Bradley, *In Re Dillon: Prima Facie Obviousness of Chemical Claims,* 22 GOLDEN GATE U. L. REV. 263, 268 (1992).

[53] *See In re* Stemniski, 444 F.2d 581, 585–86 (C.C.P.A. 1971).

[54] *In re* Dillon, 919 F.2d 688, 696 (Fed. Cir. 1990) (en banc).

[55] *See* Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339 (Fed. Cir. 2000).

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

[57] *In re* Henze, 181 F.2d 196 (C.C.P.A. 1950).

[58] *In re* Stemniski, 444 F.2d at 587.

[59] *Hass*, 141 F.2d at 125 ("It is well understood by chemists that the members of a homologous series of chemical compounds possess the same principal

continued . . .

In *In re Hass*, the appellant filed a patent application claiming new and useful nitroolefins.[60] The patent claims were rejected by the patent examiner based on prior art that disclosed compounds with similar structure but did not disclose any similar properties.[61] The rejection was affirmed by the Patent Appeal Board, which led to the appeal to the CCPA.[62] Hass asserted that without a similar property there was no teaching that could have led a skilled artisan to the claimed invention.[63] Therefore, according to Hass, unexpected or unobvious properties should not have been required to establish patentability.[64] However, the CCPA opined that compounds with similar structures often had similar properties; therefore, a similarity in property could be inferred from a structural similarity.[65] Following this line of reasoning, the CCPA held that a prima facie case of obviousness could be established by showing a high similarity between the structure of the claimed invention and a structure in the prior art. This reasoning was later reaffirmed by the CCPA in *In re Henze*, thus leading to the Hass-Henze doctrine.[66] Once the prima facie case of obviousness is established, according to the court, "[t]he burden is on the applicant to rebut that presumption by a showing that the claimed compound *possesses* unobvious or unexpected beneficial properties not actually *possessed* by the prior art homologue."[67]

The Hass-Henze doctrine remained on the books for two decades until it was explicitly overruled by the CCPA in *Stemniski*, where the appellant's claims were rejected by the U.S. Patent and Trademark Office (the "USPTO") based on prior art that disclosed structurally similar compounds without disclosing their utilities.[68] The USPTO followed the Hass-Henze doctrine and ruled that the prima facie case

characteristics; that generally the chemical and physical properties of the individual members vary gradually from member to member; and that knowledge of the properties and chemical behavior of one of the members of the series suggests to the chemist the properties and chemical behavior of the other members of the series.").

[60] *Id.* at 122.

[61] *Id.* at 123; *see also Henze*, 181 F.2d at 201 ("[T]he nature of homologues and the close relationship the physical and chemical properties of one member of a series bears to adjacent members is such that a presumption of unpatentability arises against a claim directed to a composition of matter, the adjacent homologue of which is old in the art.").

[62] *Hass*, 141 F.2d at 123.

[63] *See id.* at 124–25.

[64] *Id.* at 125.

[65] *Id.*

[66] *Henze*, 181 F.2d at 202.

[67] *Id.* at 201 (emphasis in original).

[68] *In re* Stemniski, 444 F.2d 581, 587 (C.C.P.A. 1971).

of obviousness was established by the structural similarity between the claimed invention and the prior art and that the appellant failed to rebut the presumption of obviousness with any evidence of unexpected or unobvious properties.[69] Reversing the USPTO's decision, the *Stemniski* court questioned whether the Hass-Henze doctrine imposed the correct burden of proof for the prima facie case of obviousness and concluded that it did not.[70] Explicitly overruling the doctrine, the court announced that "*Henze*, its predecessors and its progeny have met with their share of criticism over the years" and that "progress in the *useful* arts is ill-served by denying patents to inventors" following the Hass-Henze doctrine.[71]

B. The Modern Obviousness Analysis for Chemical Compounds

The general interpretation of *Stemniski* is that, in addition to structural similarity, a teaching in the prior art is required to establish a prima facie case of obviousness. This interpretation has sometimes led to extreme decisions. To clarify its position, the CAFC rendered an *en banc* decision in *In re Dillon*, which is considered the most current case law in obviousness-type, claim validity analysis based on structural similarity of chemical compounds.[72] In that case, the CAFC affirmed the judgment of the Board of Patent Appeals and Interferences (the "BPAI") rejecting certain claims in Dillon's patent application covering fuel additives.[73] According to the court, Dillon failed to overcome the presumption of obviousness, which was established based on the prior art that gave reason or motivation for a skilled artisan to make the claimed invention.[74]

Dillon's patent described the discovery that adding certain tetra-orthoester compounds to fuel could reduce the emission of solid

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[69] *Id.* at 583 ("The crux of the Patent Office position seems to be, in other words, that where a prima facie case of obviousness of claimed compounds has been established by reason of close structural similarity to prior art compounds, and that case has not been rebutted by any evidence of unexpected or unobvious properties inhering in those novel compounds which do not *actually* or *in fact* inhere in the structurally related compounds of the principal prior art references, the rejection is proper under § 103, *even though* those in the art at the time appellant's invention was made may be unaware of *any* significant properties or uses possessed by the prior art compounds." (emphasis in original)).

[70] *Id.* at 587.

[71] *Id.* (emphasis in original).

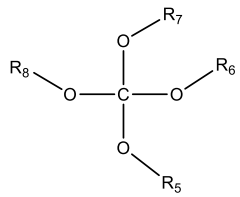
[72] *See In re* Dillon, 919 F.2d 688, 698 (Fed. Cir. 1990) (en banc).

[73] *Id.*

[74] *Id.*

particles during combustion.[75] In its broadest composition claim, Dillon claimed a composition comprising a hydrocarbon fuel and a sufficient amount of at least one tetra-orthoester, while the broadest method claim covered the method of using such composition.[76] The BPAI rejected both the composition claim and the method claim based on the prior art, shown in Table 1.[77]

Table 1. Comparison of the prior art and the claimed invention:

Prior art:	Claimed invention:
1. Tetra-orthoesters were a known class of compounds.[78] 2. Tri-orthoesters were known to be used for "dewatering" fuels.[79] 3. Tri-orthoesters and tetra-orthoesters were known to be used as water scavengers in hydraulic (non-hydrocarbon) fluids.[80]	Adding tetra-orthoesters to fuel can reduce solid particle emissions during combustion.[81] 

The CAFC stated that a prima facie case of obviousness for a compound claim could be established by structural similarity between the claimed compound and the compound(s) in the prior art, if the prior art gave reason or motivation for a skilled artisan to make the claimed compound.[82] Explicitly reversing the panel decision and overruling its prior holding in a non-compound case, *In re Wright*,[83] the CAFC clarified that a prima facie case of obviousness did not

[75] *Id.* at 690.
[76] *Id.* at 690-91.
[77] *Id.* at 690.
[78] *Id.* at 691.
[79] *Id.*
[80] *Id.*
[81] *Id.* at 690.
[82] *See id.* at 692 ("[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." (emphasis in original)).
[83] *See In re* Wright, 848 F.2d 1216, 1219 (Fed. Cir. 1988) (stating that a prima facie case of obviousness requires that the prior art suggest the claimed composition's properties and the problem the applicant attempts to solve).

require showing in the prior art a suggestion or expectation that the claimed compound would have the same or similar utility as the one newly discovered by the applicant.[84] The CAFC announced that "the statement that a *prima facie* obviousness rejection is not supported if no reference shows or suggests the newly-discovered properties and results of a claimed structure is not the law."[85]

Turning to the specific facts in *In re Dillon*, the court concluded that a prima facie case of obviousness had been established because the prior art provided the motivation to make the claimed composition, a fuel with a tetra-orthoester, in the expectation that they would have similar properties.[86] Dillon had an opportunity to rebut the prima facie case, the court added, but did not present any data showing unexpected superior properties.[87] Therefore, Dillon's claims on the appeal "are not structurally or physically distinguishable from the prior art compositions by virtue of the recitation of their newly-discovered use."[88]

Rejecting the dissenting judges' position that similarities of both structure and utility are required to establish a prima facie case of obviousness,[89] the majority stated that properties

> *are* relevant to the creation of a *prima facie* case in the sense of affecting the motivation of a researcher to make compounds closely related to or suggested by a prior art compound, but it is not required, as stated in the dissent, that the prior art disclose or suggest the properties newly-discovered by an applicant in order for there to be a *prima facie* case of obviousness.[90]

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[84] *In re* Dillon, 919 F.2d at 693 ("[I]t is not necessary in order to establish a *prima facie* case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from *the prior art* that the claimed compound or composition will have the same or a similar utility *as one newly discovered by applicant*." (emphasis in original)).

[85] *Id*. (emphasis in original).

[86] *Id*.

[87] *Id*.

[88] *Id.* at 693 n.4.

[89] *Id.* at 700 (Newman, J., dissenting) ("[D]etermination of whether a *prima facie* case of obviousness has been made requires consideration of the similarities and differences as to structure *and* properties and utility, between the applicant's new compounds or compositions and those shown in the prior art." (emphasis in original)).

[90] *Id.* at 697 (emphasis in original).

C. The Lead Compound Theory for Obviousness Analysis of Chemical Arts

Building on the same principle of the *Graham* factors and *In re Dillon*, the CAFC in *Yamanouchi v. Danbury* streamlined the obviousness analysis using the concept of lead compound.[91] In *Yamanouchi,* the CAFC affirmed the decision granting a motion for judgment as a matter of law ("JMOL") made by the trial court which upheld the validity of the U.S. Patent No. 4,283,408 (the "'408 patent") for famotidine.[92] Yamanouchi was the patent holder of famotidine, which was approved by the FDA for the treatment of peptic ulcer and gastroesophageal reflux.[93] Danbury, a generic drug manufacturer, filed an ANDA with a paragraph IV certification to the FDA seeking approval to market generic famotidine.[94] In the paragraph IV certification, Danbury asserted that the relevant claim of the '408 patent was invalid in light of the prior art available at the time of the invention.[95]

The central dispute of the case was whether one skilled in the art would have found motivation to combine a piece from one prior art with a piece from another prior art through a series of chemical manipulations.[96] According to Danbury, a skilled artisan would have considered it obvious to select the compound of example 44 from Yamanouchi's U.S. Patent No. 4,252,819 and tiotidine from another patent as lead compounds for making famotidine because these compounds are three and eleven times more active, respectively, than the benchmark compound at the time of invention, as shown in Table 2.[97] After selecting these two lead compounds, as asserted by Danbury, it would have been obvious for a skilled artisan to combine the polar tail from example 44 with the substituted heterocycle from tiotidine to form the intermediate compound.[98] Additionally, Danbury claimed it would also have been obvious to perform a bioisosteric substitution of the carbamoyl ($CONH_2$) group in the intermediate compound with a sulfamoyl group (SO_2NH_2) to create famotidine.[99]

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[91] Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1344-45 (Fed. Cir. 2000).

[92] *Id.* at 1340–42.

[93] *Id.* at 1341–42.

[94] *Id.* at 1342.

[95] *Id.*

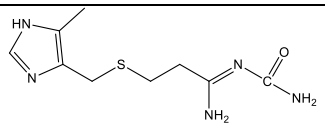
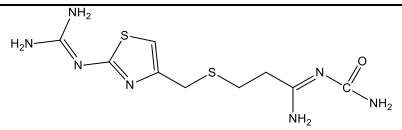
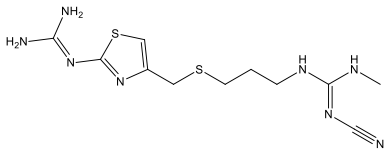
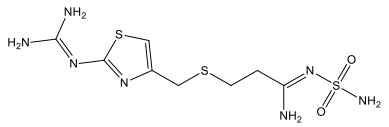
[96] *Id.* at 1343.

[97] *Id.* at 1343–44.

[98] *See id.* at 1344.

[99] *Id.*

Table 2. Comparison of prior art compounds and the claimed structure of famotidine:

Prior art	Claimed invention
 Example 44, H_2 antagonist, three times more active than the benchmark compound.	 Intermediate compound, combining the urea tail of example 44 and the guanidinyl thiazol head of tiotidine.
 Tiotidine, H_2 antagonist, eleven times more active than the benchmark compound.	 Famotidine, '408 patent, H_2 antagonist, inhibit gastric acid secretion.

Applying the *Graham* factors and *In re Dillon* to the facts of the *Yamanouchi* case, however, the CAFC pointed out that Danbury did not show the required motivation to select example 44 as a lead compound.[100] According to Danbury, the motivation existed because example 44 was three times more active than cimetidine, which was used as the benchmark compound.[101] However, as noted by the court, activity alone did not provide sufficient motivation because other prior art references disclosed compounds with H_2 antagonist activity up to ten times higher than cimetidine.[102] "If activity alone was the sole motivation, other more active compounds would have been the obvious choices, not example 44."[103]

Also based on the facts in the case, according to the CAFC panel, Danbury failed to show the motivation to modify the lead compound to the claimed invention.[104] Danbury argued that an ordinary medicinal chemist would have reasonably expected the resulting compound to exhibit the baseline level of H_2 antagonist activity

[100] *Id.* at 1345.
[101] *Id.*
[102] *Id.*
[103] *Id.*
[104] *See id.*

because of the structural similarity.[105] The baseline level of activity for the asserted lead compound is a mere 1/165th of the activity of the benchmark compound and the court reasoned that this percentage does not support a reasonable expectation of success.[106] The CAFC panel reasoned that the success of the compound was not from discovering one of the tens of thousands of compounds that exhibit baseline H_2 antagonist activity, but rather "finding a compound that had high activity, few side effects, and lacked toxicity."[107]

Yamanouchi was the first case in which the CAFC panel formulated the obviousness analysis for chemical compound claims in terms of a lead compound: to establish a prima facie case of obviousness for a compound claim, it must be obvious for a skilled artisan to select the prior art compound as a lead compound and to modify the lead compound to the claimed invention, thus the lead compound theory.[108] This theory reflects the general principle of obviousness analysis established in *Graham v. John Deere* and is consistent with the CAFC's holding in *In re Dillon*.[109] As will be discussed in the following section, this theory survived *KSR* and has been applied in all obviousness-type invalidity cases for chemical compounds.

V. RECENT CACF CASES APPLYING THE LEAD COMPOUND THEORY

This section will survey chemical compound cases decided by the CAFC since *Yamanouchi*, with special attention paid to those showing high structural similarity between the prior art and the claimed invention. As will be shown through those cases, the CAFC closely followed the lead compound theory in the obviousness analysis, especially the motivation requirement. So far, none of the generic manufacturers challenging the validity of NDA compound patents were able to satisfy the motivation requirement of the lead compound theory.

A. Eli Lilly v. Zenith Goldline

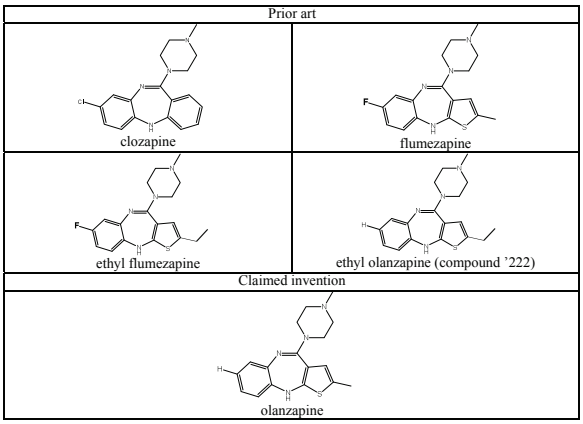
Decided in December 2006, *Eli Lilly v. Zenith Goldline* is a pre-*KSR* case, in which the CAFC applied the lead compound theory and

[105] *See id.*
[106] *Id.*
[107] *Id*.
[108] *See id.*
[109] *See In re* Dillon, 893 F.2d 1554, 1559–60, 1569 (Fed. Cir. 1989) (en banc); Graham v. John Deere, 383 U.S. 1 (1966).

affirmed the decision by the U.S. District Court for the Southern District of Indiana, upholding the validity of Eli Lilly's patent, U.S. Patent No. 5,229,382 (the "'382 patent").[110]

The '382 patent claims olanzapine, the active ingredient of Zyprexa®, approved by the FDA for the treatment of schizophrenia.[111] Zenith Goldline Pharmaceuticals, Dr. Reddy's Lab and Teva Pharmaceuticals (collectively referred to as "DRL" because the invalidity defense was asserted by Dr. Reddy's Lab) sought FDA approval to market generic olanzapine by filing an ANDA, which triggered an infringement action by Eli Lilly.[112] As part of the response to Eli Lilly's infringement suit, DRL challenged the validity of the '382 patent by asserting that the claim for olanzapine was obvious to a skilled artisan based on the prior art known at the time of the invention, such as flumezapine, ethyl flumezapine, and ethyl olanzapine, as shown in Table 3.[113]

Table 3. Comparison of the prior art and olanzapine:



DRL asserted that the prior art identified and disclosed compounds with the same biological utility in the same structural family as olanzapine, namely thienobenzodiazepines, such as clozapine, flumezapine, ethyl flumezapine, and ethyl olanzapine.[114] The only difference between olanzapine and one of the prior art compound, ethyl olanzapine, is the methyl substitution for olanzapine versus the

[110] Eli Lilly & Co. v. Zenith Goldline Pharm., 471 F.3d 1369, 1383 (Fed. Cir. 2006).

[111] *Id*. at 1373.

[112] *Id.*

[113] *See id.* at 1374-75.

[114] *Id.* at 1374, 1376.

ethyl substitution for ethyl olanzapine at the same position.[115] Using *In re Petering*[116] and *In re Schaumann*[117] as support, IVAX (formerly Zenith Goldline Pharmaceuticals) argued that olanzapine, as claimed in the '382 patent, was anticipated by the broader and inclusive genus disclosed in the prior art.[118]

Distinguishing the *Eli Lilly* case from *In re Petering* and *In re Schaumann*, the CAFC panel focused on the size of the genus disclosed in the prior art.[119] As pointed out by the court, "[i]n *Petering*, the prior art disclosed a limited number of specific preferences from a specifically defined group of isoalloxazines. As a result, *Petering* actually disclosed to one skilled in the art a limited class of only 'some 20 compounds . . . .'"[120] "Similarly, the prior art in *Schaumann* disclosed 14 compounds, later further narrowed to 7, considering express preferences. Additionally, the structural formula of this prior art contained but a single variable."[121] On the contrary, as emphasized by the CAFC panel, the prior art in *Eli Lilly* disclosed millions of compounds, including all proposed alternative substituents.[122]

Applying the lead compound theory to the *Eli Lilly* case, the CAFC panel affirmed the district court's decision that the prior art did not support the identification of any prior art compound as the lead compound.[123] While the court recognized that the structure of olanzapine is very similar to structures of several prior art compounds, it focused on the fact that the SAR in the prior art "expressed a preference for halogen-containing compounds (fluorine or chlorine), not hydrogen."[124] Even in the patent that disclosed ethyl olanzapine, the SAR "expressed a *preference* for halogen containing compounds and specifically those with a halogenated substituent on the benzene ring in a location analogous to the chlorine in clozapine."[125] Therefore, the court concluded:

> [T]he defendants have not shown that a person ordinarily skilled in this art would have selected

[115] *See id.* at 1374–76.
[116] *In re* Petering, 301 F.2d 676, 682 (C.C.P.A. 1962).
[117] *In re* Schaumann, 572 F.2d 312, 315 (C.C.P.A. 1978).
[118] *Eli Lilly*, 471 F.3d at 1376.
[119] *Id.*
[120] *Id.* (citation omitted).
[121] *Id.*
[122] *Id.*
[123] *Id.* at 1378–79.
[124] *See id.* at 1376.
[125] *Id.* at 1378 (emphasis in original).

> compound '222 as a lead compound because it contained hydrogen rather than fluorine or chlorine. At the time of invention, the state of the art would have directed the person of ordinary skill in the art away from unfluorinated compounds like compound '222.[126]

Relying on the same SAR, the CAFC held that "the prior art also did not suggest any of the other modifications necessary to reach olanzapine."[127] As reasoned by the court, "mere identification in the prior art of each component of a composition does not show that the combination as a whole lacks the necessary attributes for patentability, i.e. is obvious."[128] In order to establish a prima facie case of obviousness based on a combination of known elements in the prior art, a motivation is required to select the lead compound and to modify the lead compound to the claimed invention.[129] The SAR in the *Eli Lilly* case, according to the CAFC, did not support such a motivation.[130]

B. Takeda v. Alphapharm

In June 2007, the CAFC rendered its first post-*KSR* opinion regarding the obviousness-based invalidity for chemical compounds, *Takeda v. Alphapharm*, in which the CAFC panel affirmed the district court's decision by upholding the validity of U.S. Patent No. 4,687,777 (the "'777 patent").[131]

Takeda owns the '777 patent which covers pioglitazone, a PPAR-γ agonist and the active ingredient of Actos®, approved by the FDA for type-2 diabetes.[132] Alphapharm filed an ANDA for Actos® and, in response to Takeda's infringement suit, alleged that the '777 patent was invalid due to obviousness in light of the prior art available at the time of the invention, as shown in Table 4.[133] More specifically, Alphapharm asserted that pioglitazone would have been obvious over compound b, which the district court found that Alphapharm failed to prove by clear and convincing evidence.[134]

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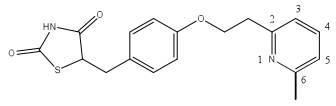
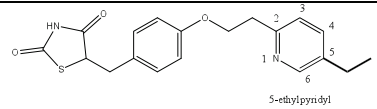
[126] *Id.* at 1379.
[127] *Id.*
[128] *Id.*
[129] *See id.*
[130] *See id.* at 1380.
[131] *See* Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1364 (Fed. Cir. 2007).
[132] *Id.* at 1352-54.
[133] *Id.* at 1353-54.
[134] *Id.* at 1354.

Table 4. Comparison of the prior art and the claimed invention:

Prior art	Claimed invention
 compound b	 pioglitazone

Rejecting Alphapharm's assertion that *KSR v. Teleflex* and *Pfizer v. Apotex* mandated reversal in this case, the CAFC reaffirmed its analysis for chemical compound cases in *In re Grabiak*,[135] *In re Dillon,*[136] *In re Jones*,[137] and *In re Deuel*.[138] According to the *Takeda* court,

> [w]hile the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination.[139]

Moreover, stated by the *Takeda* court, the idea underlying the TSM test is consistent with the *Graham* analysis and can provide

[135] *Id.* at 1356 ("In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." (citing *In re* Grabiak, 769 F.2d 729, 731–32 (Fed. Cir. 1985))).

[136] *Takeda*, 492 F.3d at 1356 ("[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." (citing *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990))).

[137] *Takeda*, 492 F.3d at 1356 ("[I]n order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required." (citing *In re* Jones, 958 F.2d 347 (Fed. Cir. 1992))).

[138] *Takeda*, 492 F.3d at 1356 ("[N]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound" because "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." (citing *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995))).

[139] *Takeda*, 492 F.3d at 1356–57 (citing KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1731 (2007)).

helpful insight for an obviousness inquiry, as long as the test is not applied as a rigid and mandatory formula.[140] Therefore, the *Takeda* court held that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[141]

Turning to pioglitazone, the CAFC panel agreed with the trial court that nothing in the evidence would have made it obvious for a skilled artisan to select compound b as a lead compound for further optimization.[142] Compound b was disclosed in a patent which covered "hundreds of millions of TZD [thiazolidinedione] compounds."[143] Although test results of nine compounds, including compound b, were provided to the USPTO during the patent examination, the *Takeda* court found nothing in the patent or its filing history "to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties."[144] On the contrary, in another cited publication, compound b was not selected as one of the three most favorable compounds, but rather singled out as causing "considerable increase in body weight and brown fat weight."[145] Therefore, the court concluded that Alphapharm did not make out a prima facie case of obviousness and that the relevant patent claims were valid.[146]

Based on the analysis of the *Takeda* case, a prima facie case of obviousness cannot be established when (1) the prior art offered a broad range of compounds and did not give any reason to select any particular one for further modification; (2) the prior art taught away from using the asserted lead compound; and (3) there was no reasonable expectation of success to modify the lead compound to the claimed invention.[147]

C. Eisai v. Dr. Reddy's Lab

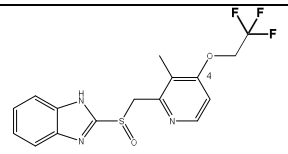
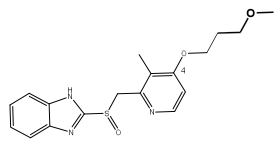
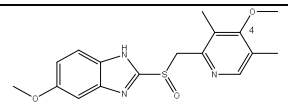
In July 2008, the CAFC affirmed the summary judgment decision

[140] *Takeda*, 492 F.3d at 1357.
[141] *Id.*
[142] *Id.*
[143] *Id.*
[144] *Id.*
[145] *Id.* at 1358.
[146] *Id.* at 1362–63.
[147] *See id.*

of the U.S. District Court for the Southern District of New York and upheld the validity of Eisai's U.S. Patent No. 5,045,552 (the "'552 patent") against the obviousness challenge brought by Dr. Reddy's Lab and Teva Pharmaceuticals.[148]

The '552 patent claims rabeprazole, an H^+K^+ATPase inhibitor and the active ingredient for Aciphex®, which was approved by the FDA to treat duodenal ulcers, heartburn, and associated disorders.[149] Dr. Reddy's Lab and Teva each filed an ANDA for generic Aciphex® and alleged that the '552 patent was invalid because it was obvious to a skilled artisan at the time of the invention in light of the prior art, such as lansoprazole and omeprazole, as shown in Table 5.[150]

Table 5. Comparison of the prior art and the claimed invention:

Prior art	Claimed invention
 lansoprazole	 rabeprazole
 omeprazole	

Reaffirming its pre-*KSR* decisions in chemical compound cases including the lead compound theory, the CAFC panel in *Eisai v. Dr. Reddy's Labs* noted that a prima facie case of obviousness for a chemical compound "requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.'"[151] "Obviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a

[148] Eisai Co. v. Dr. Reddy's Labs., 533 F.3d 1353, 1362 (Fed. Cir. 2008). The Court also noted that while both Reddy and Teva asserted the unenforceability due to inequitable conduct Teva further argued that the patent was invalid due to obviousness.

[149] *Id.* at 1356.

[150] *Id.* at 1356–57.

[151] *Id.* at 1357 (quoting *In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)).

particular way to achieve the claimed compound."[152]

Turning to the specific facts in the *Eisai* case, the court analyzed the prior art proffered by Teva including lansoprazole, omeprazole, and a scientific article describing the SAR of compounds with the same scaffold.[153] Viewing the evidence most favorable to Teva, according to the CAFC panel, lansoprazole was twenty times more active than omeprazole and had certain more desirable features.[154] Therefore, "one of skill in this art may have considered it a candidate for a lead compound in the search for anti-ulcer compounds."[155]

However, the court could find no support in the evidence that would have motivated a person skilled in the art to modify the lansoprazole toward rabeprazole.[156] As recognized by the court, lansoprazole differed from rabeprazole mainly in its trifluoroethoxy (OCH_2CF_3) substitution at the 4-position on the pyridine ring,[157] and omeprazole differed from rabeprazole even more with its methoxy (OCH_3) substitution at the pyridine ring 4-position.[158] As testified by a Teva expert, there existed a prior art teaching that "fluorine-substituted groups increase lipophilicity,"[159] which is considered a desirable feature to a skilled artisan. However, rabeprazole does not retain this trifluoroethoxy group, which, in fact, is the only difference between lansoprazole and rabeprazole.[160] As pointed out by the court, the record "shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property."[161] Therefore, the court did not believe that a case of obviousness had been established, as a matter of law.[162]

The teaching of the case is that any compound may serve as a lead compound if there is a reason for a skilled artisan to start with the

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[152] *Eisai*, 533 F.3d at 1357 (citing *Takeda*, 492 F.3d at 1356).

[153] *See Eisai*, 533 F.3d at 1357.

[154] *Id.* at 1358 (stating that "lansoprazole is twenty times superior to omeprazole for anti-ulcer action, as measured by an indomethacin-induced gastric lesion assay in rats. This court also assumes that lansoprazole has certain traits, including lipophilicity (the ability of a compound to cross lipid membranes) and low molecular weight, that would have made it desirable to a skilled artisan.").

[155] *Id.*

[156] *Id.*

[157] *Id.* at 1357.

[158] *Id.*

[159] *Id.* at 1358.

[160] *See id.* at 1357.

[161] *Id.* at 1358.

[162] *Id.* at 1359.

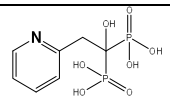
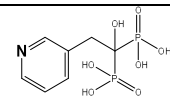
compound and modify it toward the claimed compound.[163] However, the modification would not be obvious if the prior art did not show any reason to motivate the particular modification leading to the claimed compound, especially when the prior art taught that the particular modification would destroy its desirable properties.

D. Procter & Gamble v. Teva

In May 2009, the CAFC panel affirmed a decision by the U.S. District Court for the District of Delaware upholding the validity of U.S. Patent No. 5,583,122 (the "'122 patent") against the challenge for obviousness-type double patenting.[164]

The '122 patent relates to risedronate acid, the active ingredient in Actonel® approved by the FDA for the treatment of osteoporosis.[165] After Teva Pharmaceuticals filed an ANDA for generic risedronate, Procter & Gamble ("P & G") filed suit against Teva for patent infringement.[166] In response, Teva asserted that the '122 patent was invalid due to obviousness in light of the prior art disclosed in P & G's expired patent (U.S. Patent No. 4,761,406), particularly 2-pyr etidronate (EHDP), as shown in Table 6.[167]

Table 6. Comparison of the prior art and risedronate:

Prior art	Claimed invention
	
2-pyr EHDP	risedronate acid, 3-pyr EHDP

The CAFC panel recognized that an obviousness argument based on structural similarity depends on a preliminary finding that a skilled artisan would have selected the prior art compound as a lead compound.[168] However, the court did not feel it was necessary to reach this question because the evidence showed that even if a skilled artisan could have identified 2-pyr EHDP as a lead compound, it

[163] *See id*. at 1357 (citing Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007)).

[164] Procter & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 999 (Fed. Cir. 2009).

[165] *Id.* at 992.

[166] *Id.*

[167] *Id.* at 992–93.

[168] *See id.*

would not have been obvious to one skilled in the art at the time of the invention to modify it to create risedronate (3-pyr EHDP).[169] The court found that despite the fact that 2-pyr EHDP and risedronate are positional isomers with highly similar structures, the SAR in the evidence did not show, and Teva failed to establish, sufficient motivation for a skilled artisan to make such modification.[170]

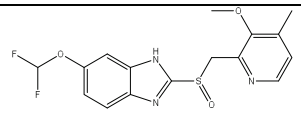
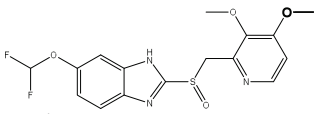
E. Altana Pharma v. Teva

In May 2009, the CAFC affirmed the decision by the U.S. District Court for the District of New Jersey denying Altana Pharma's motion for preliminary injunction to prevent Teva Pharmaceuticals from marketing a generic version of pantoprazole (trade name: Protonix® in the U.S.) for treatment of erosion and ulceration of the esophagus.[171]

Altana Pharma's pantoprazole, a proton pump inhibitor (PPI), is covered by its U.S. Patent No. 4,758,579 (the "'579 patent").[172] After Teva filed an ANDA seeking FDA approval of a generic version of pantoprazole, Altana Pharma filed an infringement suit and a motion for preliminary injunction.[173] While it conceded infringement, Teva maintained that the '579 patent was invalid due to obviousness in light of several prior art teachings, especially compound 12 from Altana Pharma's earlier patent (U.S. Patent No. 4,555,518, the "'518 patent"), as shown in Table 7.[174] Upon hearing Altana Pharma's motion for preliminary injunction, the District Court found that the defendants had demonstrated a substantial question of invalidity.[175] "In particular, the court found that one of skill in the art would have selected compound 12 as a lead compound for modification."[176]

Table 7. Comparison of the prior art and pantoprazole:

[169] *Id.* at 994–95.
[170] *Id.* at 995–96.
[171] Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1000, 1002–04, 1011 (Fed. Cir. 2009).
[172] *Id.* at 1002.
[173] *Id.* at 1004.
[174] *Id.*
[175] *Id.*
[176] *Id.* at 1004–05.

Prior art	Claimed invention
 compound 12 in ’518 patent	 pantoprazole

In the portion of the *Altana Pharma* court’s opinion on likelihood of success on the merits, the court pointed out several pieces of evidence supporting the finding that a skilled artisan would have selected compounds disclosed in the ’518 patent, especially compound 12, as a lead compound for further development.[177] First of all, the ’518 patent claimed that its compounds were improvements over the prior art, specifically omeprazole (the first successful PPI).[178] Second, compound 12 was “one of the more potent of the eighteen compounds of the ’518 patent for which data was provided during prosecution.”[179] As stated by the court, “[a]lthough potency is not dispositive, the district court believed—not unreasonably—that the potency of the compound was a factor that would have led one of skill in the art to select compound 12 from the group for further study.”[180]

Despite the limited precedential value of *Altana Pharma* due to its procedural posture,[181] one teaching from the case is that to establish a prima facie case of obviousness the prior art need not identify a sole lead compound.[182] The CAFC panel clearly rejected Altana Pharma’s suggestion that “the prior art must point to only a single lead compound for further development efforts.”[183] In CAFC’s opinion, this “restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*.”[184]

While *Altana Pharma* is one of the closest cases where the CAFC may hold a chemical compound patent invalid due to obviousness, it is important to note that an “appellant carries a heavier burden when

[177] *Id.*

[178] *Id.* at 1007.

[179] *Id.* at 1007–08.

[180] *Id.* at 1008.

[181] When appealing a denial of a preliminary injunction, the appellant must show that part of the decision of denial was based on a clearly erroneous finding, and that the trial court’s denial of the injunction constituted an abuse of discretion.

[182] *See Altana Pharma* 566 F.3d at 1007–08.

[183] *See id.* at 1008.

[184] *Id.*

seeking to reverse the denial of a preliminary injunction than seeking to reverse the grant of a preliminary injunction."[185] Moreover, this decision also heavily hinged on the fact that discretionary weight must be given to a district court's decision. As noted in Judge Newman's concurring opinion, "[a]lthough the evidence presented to the district court does not . . . establish invalidity of the patent on the pharmaceutical product pantoprazole, at this preliminary stage deference is warranted to the district court's weighing of the conflicting expert opinions interpreting the evidence."[186] This comment highlights the possibility that the outcome of this case could have been completely different had the review been solely based on the determination of obviousness for the patent-at-issue.

F. *Daiichi v. Matrix Labs*

In 2010, the CAFC affirmed the decision of the U.S. District Court for the District of New Jersey that Matrix Labs failed to establish a prima facie case of obviousness and upheld the validity of U.S. Patent No. 5,616,599 (the "'599 patent")[187] for olmesartan medoxomil (trade name: Benicar® in the U.S.), an angiotensin receptor blocker (ARB) approved by the FDA for treatment of high blood pressure (hypertension).[188]

The discovery of olmesartan medoxomil as an effective ARB for hypertension was built on years of research beginning in the 1970s.[189] More than 200 structurally-related ARBs were disclosed in the losartan patent (U.S. Patent No. 5,138,069, the "'069 patent") and DuPont's U.S. Patent No. 5,137,902 (the "'902 patent").[190] The compound bearing the highest structural similarity to olmesartan is example 6 from the '902 patent, as shown in Table 8, differing by only a single oxygen atom at the 4-position of the imidazole ring.[191] Based on this structural similarity, Matrix Labs and other defendants challenged the validity of the olmesartan patent asserting that it was obvious to a skilled artisan in light of the prior art known at the time of

[185] *Id.* at 1005.

[186] *Id.* at 1011 (Newman, J., concurring) (citation omitted).

[187] Daiichi Sankyo Co., v. Matrix Labs., 619 F.3d 1346, 1357 (Fed. Cir. 2010).

[188] *Id.* at 1347.

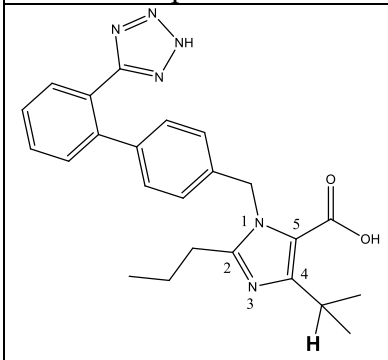
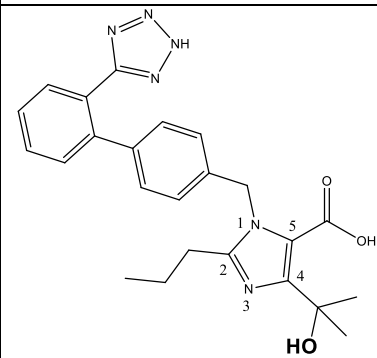
[189] *Id.* at 1348–49 (stating losartan was developed by DuPont and disclosed "in U.S. Patent 5,138,069 (the '069 patent') along with more than four hundred structurally related ARBs.").

[190] *See id.* at 1349–50.

[191] *Id.* at 1350–51.

the invention.[192]

Table 8. Comparison of the prior art and the claimed invention:

The closest prior art	Claimed invention
	
example 6 The '902 patent, DuPont	olmesartan

Applying the lead compound theory to olmesartan, the CAFC panel agreed with the trial court that the SAR for all ARBs in the prior art did not make it obvious for a skilled artisan to select one of the compounds in the '902 patent bearing high similarity with olmesartan as a lead compound.[193] In selecting a lead compound for further development, a skilled artisan depends on not only structural similarity, but also knowledge of SARs among prior art compounds.[194] According to the CAFC panel, based on SARs disclosed in the prior art and a rich collection of testing data, compounds in the '902 patent did not stand out as an obvious choice of a lead compound.[195] As the

[192] *See id.* at 1351 (One of the defendants, Mylan, alleged in a counterclaim that: (1) one of skill in the art would have been motivated to select ARBs in DuPont's '902 patent as lead compounds; (2) Example 118 in DuPont's '069 patent would have motivated one of skill in the art to modify the '902 compounds' lipophilic alkyl groups at the 4-position with olmesartan's hydrophilic hydroxyalkyl group; and (3) the use of medoxomil as a prodrug was well-known.).

[193] *See id.* at 1353 ("[A] medicinal chemist of ordinary skill would not have been motivated to select the '902 compounds over other second-generation ARBs, including L-158,809, DuP 532, the Eisai compounds, and valsartan, because many of the latter ARBs demonstrated greater potency and all had been more thoroughly studied than the '902 ARBs.").

[194] *See id.* at 1354 ("[P]roving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds. Potent and promising activity in the prior art trumps mere structural relationships." (citation omitted)).

[195] *See id.* at 1353–54 (The CAFC pointed out not only oral activity, but also

continued . . .

CAFC stated, "[p]otent and promising activity in the prior art trumps mere structural relationships."[196]

The court also relied on the SAR to decide whether a skilled artisan would have had a motivation to modify the structure to olmesartan from the lead compound asserted by the defendant.[197] Specifically, the SAR indicated that at the 4-position of the imidazole ring, a lipophilic group was preferred.[198] This SAR led away from olmesartant, which has a hydrophilic group at this position.[199] Therefore, the CAFC panel concluded that structures and activity data in the prior art "counter any notion that one of skill in the art would have been motivated to modify the '902 compounds' lipophilic alkyl groups to a hydrophilic group. Such a holding would have been based on hindsight."[200]

G. Otsuka v. Sandoz

The latest case from the CAFC regarding the obviousness standard of a chemical compound claim is *Otsuka Pharm. Co. v. Sandoz, Inc.* Decided on May 7, 2012, the CAFC affirmed the district court's finding of validity, holding that the compound at issue, aripiprazole, was not obvious to a skilled artisan in light of prior art compounds, as shown in Table 9.[201]

Aripiprazole (trade name: Abilify®) is an atypical antipsychotic and antidepressant approved by the FDA for the treatment of schizophrenia.[202] Unlike "typical" antipsychotics that only treat positive symptoms of schizophrenia, those that treat both positive and negative symptoms are referred to as "atypical" antipsychotics.[203] Since the approval of clozapine in 1990 and risperidone in 1994, seven other atypical antipsychotics have been approved, among which aripiprazole is the only compound that is not structurally related to either clozapine or risperidone.[204]

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data on the binding affinity and intravenous activity for other prior art compounds).

[196] *Id.* at 1354.

[197] *Id.*

[198] *Id.* at 1355.

[199] *Id.* at 1354.

[200] *Id.*

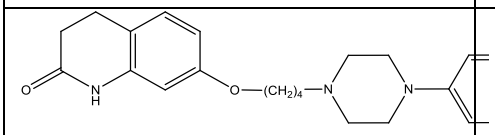
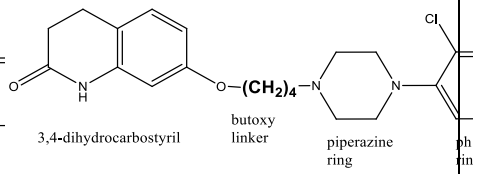
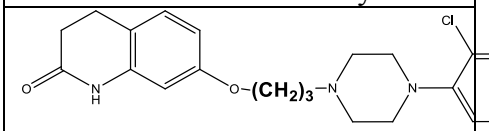
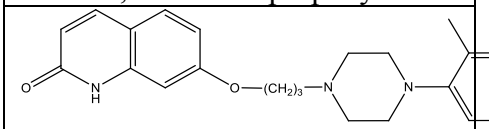
[201] Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1280, 1285-86, 1288-89 (Fed. Cir. 2012).

[202] *Id.* at 1284.

[203] *Id.*

[204] *Id.*

Table 9. Comparison of the prior art and aripiprazole:

Prior art	Claimed invention
 Prior art 1 unsubstituted butoxy	 aripiprazole
 Prior art 2 2,3-dichloro propoxy	
 Prior art 3 OPC-4392	

As shown in Table 9, various aspects of aripiprazole existed in prior art compounds that have the same scaffold. The structure of prior art 1 is identical to aripiprazole,[205] except that it is missing the dichloro substitution on the phenyl ring, which is exhibited in prior art 2.[206] Prior art 3 has a similar structure to aripiprazole but with a shorter linker (propoxy instead of butoxy) and two methyl substitutions in lieu of two chloro substitutions on the phenyl ring.[207]

Closely following the two-step inquiry in the lead compound theory, the court analyzed the SAR of prior art compounds. The CAFC panel recognized that the trial record provided nine compounds with either propoxy linker (3 carbons) or butoxy linker (4 carbons).[208] The court noted that "[o]f the nine carbostyril test compounds for which the Nakagawa declaration supplied mouse jumping data, the unsubstituted butoxy was inferior to four other test compounds and thus 'was only of middling potency.'"[209] Therefore, the court agreed with the expert that "if a skilled artisan were to select any compound from the Nakagawa declaration, it would be Compound 44," the one

[205] *See id.* at 1285–86.
[206] *See id.* at 1290.
[207] *See id.* at 1288–89.
[208] *See id.* at 1287–88.
[209] *Id.* at 1294.

with propoxy instead of a butoxy linker.[210] Therefore, the SAR did not provide a reason or motivation for a skilled artisan to select a compound with a butoxy linker as a lead compound or modify a propoxy linker in a lead compound to a butoxy linker.[211] Without such reason or motivation, the CAFC panel held no prima facie case of obviousness had been established.[212]

As shown in this section, some cases introduced prior art compounds bearing very high structural similarity to the claimed invention, such as a methyl substitution in olanzapine versus an ethyl substitution at the same location in a prior art compound, 3-pyridine in risedronate versus 2-pyridine in the prior art, and a butoxy linker in aripiprazole versus a propoxy linker in the prior art. Notwithstanding such high structural similarity, none of these were able to establish a prima facie case of obviousness. Underlining this seemingly insurmountable obstacle is the assumed unpredictability of chemical compounds.

VI. THE PREDICTABILIY OF CHEMICAL COMPOUNDS

As shown in previous sections, the modern obviousness analysis for chemical arts and the lead compound theory are largely based on the assumption that properties of chemical art are unpredictable. Accordingly, similar structures do not necessarily lead to similar properties and a minor structural modification may cause a significant and unpredictable change in properties. As will be discussed in this section, however, not all properties of chemical art are equally unpredictable. Certain properties are more predictable than others and various technologies are available to make such predictions.

A. Some Properties of Chemical Compounds Can Be Predicted Based on Physical Chemical Principles

Although properties of chemical arts are not as predictable as mechanical arts, some properties can still be predicted with reasonable accuracy. This subsection will review some popular approaches to predict properties of chemical compounds based on physical chemical principles and the applications of such predictions in pharmaceutical development.

Many molecular properties including 3D molecular structures can

[210] *See id.*
[211] *See id.* at 1292–93.
[212] *See id.* at 1296.

be calculated through quantum mechanics.[213] Purely based on its molecular formula, one can calculate molecular orbitals, their relative energies,[214] electronic configurations and their relative stabilities,[215] aromatic features, [216] and chemical reactivity of a chemical compound.[217] All quantum mechanics calculations are based on the Schrödinger equation.[218] While an analytical solution may not be available for most drug-like molecules due to their sizes, various numerical methods make quantum mechanics calculations feasible for drug design.[219]

Similarly, various molecular properties can be calculated using the molecular mechanics force field method.[220] "Force field calculations rest on the fundamental concept that a ball-and-spring model may be used to approximate a molecule."[221] In this model, the positions of atoms in a molecule are "a function of through-bond and through-space interactions, which may be described by relatively simple mathematical relationships." [222] Based on this mathematical relationship, a geometry optimization can be carried out to calculate 3D structures of a molecule with different conformations.[223] Also, based on this mathematical relationship, molecular dynamics simulations can be carried out to study molecular motions and predict macroscopic properties of a molecule.[224]

Modern chemistry is largely based on rules and predictability of chemical properties. For example, reaction rates and equilibrium constants of certain classes of organic reactions can be calculated using the famous Hammett equation, which holds true for hundreds of

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[213] *See* J. PHILLIP BOWEN, *Computational Chemistry and Computer-Assisted Drug Design*, *in* ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY 919, 935 (John H. Block & John M. Beale, Jr. eds., 11th ed., 2004).

[214] *See id.*

[215] *See id.*

[216] *See id.*

[217] *See id.*

[218] *See* Feliks Aleksandrovič Berezin & Mihail Aleksandrovič Šubin, THE SCHRÖDINGER EQUATION 3, 6 (Yu. Rajabov, D. A. Leites, & N. A. Sakarova trans., Kluwer Academic Publishers Group 1991) (1983).

[219] *See generally* J. Phillip Bowen, *Computational Chemistry and Computer-Assisted Drug Design*, *in* ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY 919, 935–39 (John H. Block & John M. Beale, Jr. eds., Lippincott Williams & Wilkins 11th ed., 2004).

[220] *See id.* at 923.

[221] *Id.*

[222] *Id.*

[223] *See id.* at 929–33.

[224] *See id.* at 933–35.

chemical reactions.[225] By using only two constants, one can predict the relative K_{eq} value or the relative reaction rate of a chemical reaction.[226]

Another example is the Hückel $4n + 2$ rule, which states that "to be aromatic a compound must have a molecule that contains *cyclic clouds of delocalized π electrons above and below the plane of the molecule*; further, *the π clouds must contain a total of* ***(4n + 2) π*** **elections**."[227] Aromatic compounds generally have a high degree of unsaturation, and yet are resistant to addition reactions generally characteristic of unsaturated compounds.[228] Purely based on molecular structures, the Hückel rule can be used to predict whether a compound has aromatic properties and whether a compound can undergo certain chemical reactions.[229]

In some cases, the intermolecular interaction between a drug molecule and the drug target can be predicted using a structure-based drug design approach. In one of the earlier examples that predate the use of modern computers and sophisticated software, Beddel and coworkers successfully predicted compounds that bind to the binding site of the human deoxyhaemoglobin tetramer.[230] The haemoglobin tetramer consists of two α and two β subunits.[231] Based on a wire model of the tetramer, molecules were selected based on their likelihood to fit into the model.[232] The selected molecule was proven to be able to bind with deoxyhemoglobin tetramer with enhanced binding affinity and thus it went into further pharmaceutical development.[233]

Dorzolamide was the first marketed drug resulting from structure-based drug design.[234] Dorzolamide (trade name Trusopt®) decreases the production of aqueous humor by inhibiting carbonic anhydrase, thus lowering elevated intraocular pressure in open-angle glaucoma

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[225] ROBERT THORNTON MORRISON & ROBERT NEILSON BOYD, ORGANIC CHEMISTRY, 732 (Prentice Hall 6th ed. 1992).

[226] *Id*.

[227] *Id.* at 504 (emphasis in original).

[228] *Id.*

[229] *See*, *e.g.*, *id.*

[230] *Id.* at 904.

[231] C. R. Beddel et al., *Compounds Designed to Fit a Site of Known Structure in Human Hemoglobin*, 57 BRIT. J. PHARMACOLOGY 201, 201 (1976).

[232] *See id.* at 201-08 (1976) (Reporting that three 2,3-diphosphoglycerate analogs, e.g. 4,4'-diformyl-2-bibenzyl-oxyacetic acid, bound to human deoxy-hemoglobin at the I-binding site. They promoted oxygen liberation in the predicted sequence as assessed by sigmoidal dose-response curves).

[233] *See id.* at 207.

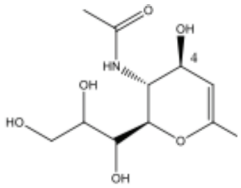
[234] Bowen, *supra* note 219, at 943.

and ocular hypertension.[235] X-ray studies and molecular models were used to predict the interaction between dorzolamide and its drug target, carbonic anhydrase, which catalyzes a reversible reaction interconverting carbon dioxide and water to and from bicarbonates.[236] Based on the predicted interaction between the drug target and potential inhibitors, suitable molecules were selected for further evaluation, one of which was dorzolamide.[237]

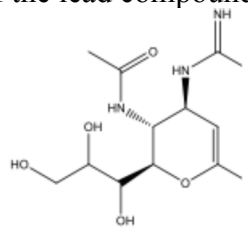
Another example of rational drug design is the research for viral neuraminidase inhibitors, which led to the discovery of Relenza® and Tamiflu®. Viral neuraminidase is a type of enzyme found on the surface of influenza viruses.[238]

When influenza viruses replicate, they bind to sialic acid groups of glycoproteins on the host cell surface.[239] To be released from the host cell, the viral neuraminidase enzymatically cleaves sialic acid groups from host glycoproteins.[240] Because the cleavage of sialic acid groups is an integral step of the influenza virus replication cycle, inhibiting the enzymatic function of viral neuraminidase is an effective way to control the replication of influenza viruses.[241]

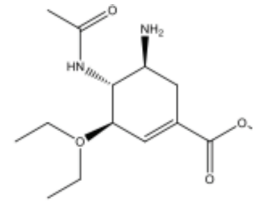
Table 10. Structures of the lead compound, zanamivir and oseltamivir:



Lead compound



zanamivir
Relenza®



oseltamivir
Tamiflu®

[235] *See* Bowen, *supra* note 219, at 943.

[236] *See* John J. Baldwin et al., Letter to the Editor, *Thienothiopyran-2-sulfonamides: Novel Topically Active Carbonic Anhydrase Inhibitors for the Treatment of Glaucoma*, 32 J. MED. CHEM. 2510, 2510–13 (1989).

[237] *Id.* (reporting that X-ray crystallographic studies with human carbonic anhydrase II-inhibitor complexes provided a basis for rationalizing the potency difference by establishing that the binding of the S isomer within the enzymic active site was clearly different from that of its R-antipode).

[238] *See* Joseph N. Varghese et al., *The Structure of the Complex Between Influenza Virus Neuraminidase and Sialic Acid, the Viral Receptor*, 14 PROTEINS: STRUCTURE, FUNCTION, & GENETICS 327, 327 (1992).

[239] *See* I-Chueh Huang et al., *Influenza A Virus Neuraminidase Limits Viral Superinfection*, 82 J. VIROLOGY 4834, 4834 (2008).

[240] *See id.*

[241] *See* Mark von Itzstein et al., *Rational Design of Potent Sialidase-Based Inhibitors of Influenza Virus Replication*, 363 NATURE 418, 418 (1993).

To guide the inhibitor design, von Itzstein and coworkers at Monash University used a structure-based drug design program, GRID, to search the surface of neuraminidase for active binding sites and predicted the nature of the interaction between neuraminidase and potential inhibitors.[242] GRID predicted that replacing the hydroxyl group at the 4-position of the lead compound, as shown in Figure 1, with a larger and more basic group would enhance the interaction between the inhibitor and the enzyme.[243] Following this prediction, a guanidinyl group (larger and more basic than hydroxyl) was introduced at the 4-position, which resulted in a 5,000-fold increase in binding affinity.[244] This new compound with a guanidinyl group, zanamivir, was the first sialidase-targeting anti-influenza drug, subsequently marketed by GlaxoSmithKline under the trade name Relenza®.[245]

The search for more neuraminidase inhibitors with properties superior to zanamivir continued under the guidance of rational drug design. Zanamivir is a very polar molecule and was delivered by means of dry-powder inhalation. Scientists at Gilead Pharmaceuticals designed a new generation of neuraminidase inhibitors by replacing the guanidinyl group with a less polar amino group and by replacing the hydrophilic glycerol chain with a lipophilic ethylpropoxy group.[246] This new design maintained all critical interactions between the inhibitor and the enzyme while significantly decreasing the polarity of the inhibitor, which was predicted to improve pharmacokinetic properties, especially absorption. Just as predicted, the modified compound had a significantly improved gastrointestinal bioavailability, which made it possible to deliver the inhibitor orally.[247] This compound, oseltamivir, was the first oral anti-influenza drug, Tamiflu®.[248]

In summary, many properties of chemical art can be calculated

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[242] *See id.* at 420.

[243] *See id.*

[244] *See id.*

[245] *See* Mark von Itzstein, *The War Against Influenza: Discovery and Development of Sialidase Inhibitors*, 6 NATURE REVS.: DRUG DISCOVERY 967, 970–71 (2007).

[246] *See* Choung U. Kim et al., *Influenza Neuraminidase Inhibitors Possessing a Novel Hydrophobic Interaction in the Enzyme Active Site: Design, Synthesis, and Structural Analysis of Carbocyclic Sialic Acid Analogues with Potent Anti-Influenza Activity*, 119 J. AM. CHEM. SOC'Y 681, 681–82 (1997).

[247] *See id.*

[248] Andrew M. Davis et al., *Application and limitations of X-ray Crystallographic Data in Structure-Based Ligand and Drug Design*, 42 ANGEWANDTE CHEMIE INT. ED. 2718, 2722 (2003).

based on physical chemical principles and rules. Some calculations are based on fundamental physical principles, such as the Schrödinger equation in quantum mechanics. Many other calculations are based on both physical chemical principles and empirically derived parameters, such as molecular mechanics calculations and structure-based design software.

B. Some Properties of Chemical Compounds Can Be Predicted Through SARs

In some cases, properties of chemical compounds cannot be reliably calculated based on fundamental physical chemical principles, but can be estimated based on intrinsic SARs of related compounds, which is the goal of quantitative structure activity relationship ("QSAR") models.

One of the most successful pioneers in the field of QSAR is Corwin Hansch who developed the Hansch equation that correlated biological activities with measurable physical chemical properties:

$$\text{Log } 1/C = -a(\log P)^2 + b \log P + p\sigma + c$$

where activity is expressed as $1/C$; C is the concentration of the drug compound required to elicit a given biological response; P is the octanol/water partition coefficient that reflects the hydrophobicity of the molecule; p is a constant featuring the molecular type of the given molecule; and σ is the Hammett substituent constant which measures the electronic effect on the rate of reaction.[249]

QSAR is widely used in computer assisted drug design. One of the most popular 3D QSAR software packages commercially available is Comparative Molecular Field Analysis ("CoMFA") developed by Richard Cramer and coworker.[250] In CoMFA, each molecule is represented by its steric field and electrostatic field in a grid box.[251] The strength of each field at each grid point can be calculated using the molecular mechanics method.[252] Therefore, each molecule can be reduced to a list of molecular descriptors.[253] This 3D QSAR model

[249] Randy J. Zauhar, *Structure-Activity Relationship and Drug Design*, *in* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY 468, 475 (Lippincott Williams & Wilkins, 21st ed. 2006).

[250] *See* Richard D. Cramer, III, et al., *Comparative Molecular Field Analysis (CoMFA): Effect of Shape on Binding of Steroids to Carrier Proteins*, 110 J. AM. CHEMICAL SOC'Y 5959, 5959 (1988).

[251] *See id.*

[252] *See id.*

[253] *See id.* at 5959–60.

can then be used to predict biological activities of other molecules.[254]

Many other QSAR programs have been developed, most of which involve various novel approaches to generate molecular descriptors used in the QSAR equation. For example, Molecular Shape Analysis ("MSA") combines the conventional Hansch QSAR approach with systematic conformation search to include conformational flexibility in the QSAR equation.[255] Comparative Molecular Similarity Indices Analysis ("CoMSIA") was developed to overcome limitations of CoMFA by including hydrophobic and hydrogen-bonding properties in the analysis.[256] Additionally, molecular descriptors were calculated by comparing similarities to a set of pre-defined molecular probes.[257] Comparative Molecular Surface Analysis ("CoMSA") is a non-grid 3D QSAR method that uses molecular surface to define molecular descriptors in the QSAR equation.[258] Adaptation of Fields for Molecular Comparison ("AFMoC") generates molecular descriptors using the protein environment with which training molecules interact, often called reversed CoMFA.[259] Comparative Molecular Moment Analysis ("CoMMA") is an alignment-independent 3D-QSAR method, which derives molecular descriptors based on spatial moments of molecular mass and charge distribution.[260]

The reliability of the QSAR prediction is critically important for its application. It is especially important to be able to estimate how well the model predicts properties of molecules outside the training set instead of how well the model reproduces properties of molecules

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[254] *Id.* at 5959, 5967.

[255] *See* A. J. Hopfinger, *A QSAR Investigation of Dihydrofolate Reductase Inhibition by Baker Triazines Based Upon Molecular Shape Analysis*, 102 J. AM. CHEMICAL SOC'Y 7196, 7196, 7205–06 (1980).

[256] T.J. Hou et al., *Three-Dimensional Quantitative Structure—Activity Relationship Analysis of the New Potent Sulfonylureas Using Comparative Molecular Similarity Indices Analysis*, 40 J. CHEMICAL INFO. & COMPUTER SCI. 1002, 1003 (2000).

[257] Yong-Qiang Zhu et al., *3D QSAR Studies of Boron-Containing Dipeptides as Proteasome Inhibitors with CoMFA and CoMSIA Methods*, 44 EUR. J. MED. CHEMISTRY 1486, 1486–87, 1494 (2009).

[258] *See* J. Polanski & B. Walczak, *The Comparative Molecular Surface Analysis (COMSA): A Novel Tool for Molecular Design*, 24 COMPUTERS & CHEMISTRY 615, 615 (2000).

[259] *See* Holger Gohlke & Gerhard Klebe, *DrugScore Meets CoMFA: Adaptation of Fields for Molecular Comparison (AFMoC) or How to Tailor Knowledge-Based Pair-Potentials to a Particular Protein*, 45 J. MED. CHEMISTRY 4153, 4154, 4168 (2002).

[260] B. D. Silverman & Daniel E. Platt, *Comparative Molecular Moment Analysis (CoMMA): 3D-QSAR Without Molecular Superposition*, 39 J. MED. CHEMISTRY 2129, 2129, 2139 (1996).

inside the training set. Various methods have been developed for this purpose. Cross-validation[261] is one the most often used methods for this purpose. It divides the whole data set into a training set and a validation set.[262] A QSAR model, constructed only based on the training set, is used to predict properties of the validation set.[263] Because molecules in the validation set were never used in the model construction, this comparison can be used to estimate how well the model can predict, rather than reproduce, molecular properties.[264]

Bootstrapping is another technique that can be used to evaluate the statistical confidence and robustness of QSAR models.[265] In bootstrapping, a large number of new datasets are constructed by randomly selecting molecules from the original set. Because redundancy is allowed during the selection process, some molecules are excluded for each new dataset. A QSAR model is built based on each new dataset. The statistical stability of all QSAR models built on all newly-generated datasets can be used to estimate the robustness of the QSAR model.[266]

In summary, certain molecular properties, including biological activities, can be predicted through SAR and QSAR methods. Numerous approaches have been developed and applied in drug discovery—especially in computer-aided drug design—and met with various successes. While the predictability of SAR and QSAR methods depends on the nature of compounds involved, especially their conformational flexibility, cross-validation techniques are available to estimate the reliability and applicability of the SAR/QSAR approach for a given project.

C. The Most Desirable Compound May Also Be Identified Through an Exhaustive Search of a Finite Number of Possible Solutions

While certain physical chemical properties can be calculated with reasonable accuracy, some other properties are predictively unpredictable. For example, in pharmaceutical research and

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[261] M. Stone, *Cross-Validatory Choice and Assessment of Statistical Predictions*, 36 J. ROYAL STAT. SOC'Y 111, 111 (1974).

[262] Lutz Prechelt, *Automatic Early Stopping Using Cross Validation: Quantifying The Criteria*, 11 NEURAL NETWORKS 761, 762 (1998).

[263] *See id.*

[264] Stone, *supra* note 261, at 111.

[265] *See* Jun Shao, *Bootstrap Model Selection*, 91 J. AM. STAT. ASSOC. 655, 655 (1996).

[266] *See id.*

development ("R&D"), it is rather difficult to reliably predict many *in vivo* properties (properties typically observed in animal studies), such as *in vivo* activities, *in vivo* pharmacokinetics properties, toxicities, and drug-drug interactions. In fact, even for those semi-predictable properties, the accuracy and reliability of predictions are limited in some cases, especially when determining the subtle differences between highly analogous structures.

Knowing this limitation, it is an ordinary practice during compound optimization in pharmaceutical R&D to expand and explore the SAR around the lead compound by synthesizing and testing analogues with similar structures. At the final stage of the compound optimization, this SAR expansion is typically done exhaustively. For example, during the course of the compound optimization of pitavastatin, a cholesterol lowering agent, a list of compounds were synthesized and tested for their inhibitory potency against HMG-CoA reductase, as shown in Table 11.[267] As recognized by the project team, the SAR suggested that "a lipophilic interaction in this region is essential in inhibiting the target enzyme."[268] Additionally, it was also recognized that the carbon length of the substitution was preferred to be around two carbon atoms.[269]

With this SAR knowledge, the project team exhaustively explored all small lipophilic groups commonly used in medicinal chemistry.[270] Although the authors could not predict which of those compounds would be the best candidate for further development, it was foreseeable that the best candidate must be among the compounds shown in the table because there was only a finite number of possible compounds with a small (around two carbons) lipophilic substitution at that position, all of which were included in the table. As predicted, one of those compounds with a small lipophilic substitution (*c*-propyl, 17jj in Table 11) showed a five-fold increase in the IC_{50} against HMG-CoA reductase and was further developed into a marketed drug, pitavastatin.[271]

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[267] Mikio Suzuki et al., *Synthesis and Biological Evaluations of Quinoline-based HMG-CoA Reductase Inhibitors*, 9 BIOORGANIC & MED. CHEMistry 2727, 2727, 2730–31 (2001).

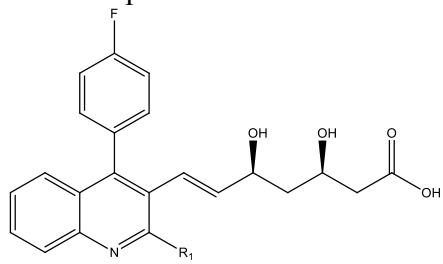
[268] *Id.* at 2730.

[269] *See id.* (stating that "inhibitory potency increased with length of the 2-substituent from methyl (**17bb**) through ethyl (**17cc**), with the greatest effect shown with isopropyl (**17ee**)," and that "increasing the length of the substituent to three carbons, *n*-propyl (**17dd**) resulted in loss of activity and showed a length limitation of the 2-substituent." (emphasis in original)).

[270] *See id.* at 2730–31.

[271] *See id.* at 2731.

Table 11. SAR table of pitavastatin:



No.	R^1	IC_{50} (nM)[c]
17aa	H	> 1000
17bb	methyl	241
17cc	ethyl	44
17dd	*n*-propyl	76
17ee	*i*-propyl	19
17ff	*n*-butyl	618
17gg	CH_2CHMe_2	71
17hh	CHMeEt	74
17ii	*t*-butyl	343
17jj	*c*-propyl	4.1
17kk	*c*-hexyl	67
17ll	phenyl	377
17mm	CF_3	140
17nn	OMe	124
17oo	SMe	484
17pp	NME_2	184
17qq	NMeEt	209

Hypothetically speaking, if compound 17aa to 17ff were available in the prior art at the time of the invention and compound 17jj was the claimed invention, would there have been a prima facie case of obviousness based on the structural similarity and the SAR? Pursuant to the Supreme Court opinion in *KSR*,

> [w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to

try might show that it was obvious under § 103.[272]

In the hypothetical case of pitavastatin, there was certainly a design need to further improve the potency of the lead compound. Because the SAR limited the size of the substitution to be shorter than three carbon lengths and the nature of the substituents to be lipophilic, only a finite number of possible functional groups (as exhibited in Table 11) can satisfy this requirement. Although it was unpredictable as to which of those small lipophilic groups would have the best substituent, the identities and structures of all possible substituents were known (predictable). Moreover, because there was no technical innovation involved to pursue each and every one of those substituents, the fact that one of the substituents was identified to be the best is arguably "not of innovation but of ordinary skill and common sense,"[273] and is thus obvious under § 103, according to *KSR*.

D. The Obviousness Analysis Based on the Lead Compound Theory Should Reflect the (Un?)predictability of Chemical Compounds

As discussed above, properties of chemical compounds are not always unpredictable. With the advancement of science and technology, more properties of more chemical compounds can be predicted more reliably, which could significantly change the obviousness analysis based on the lead compound theory. The above-mentioned technologies and approaches used to predict properties of chemical compounds have grown out of the ivory tower of theoretical chemistry and become more and more accepted by the general scientific community. As evidence of how widespread those technologies are, a key word search was carried out at the website of the Journal of Medicinal Chemistry, one of the leading scientific journals in the field of drug discovery. Various key words related to those predicting technologies were used to search the database for any article published in the Journal between January 2000 and December 2011, inclusive. The number of articles containing those key words is summarized in Table 12. Several generic key words, such as "drug," "compound," and "molecule," were also used to serve as a baseline comparison.

[272] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).
[273] *Id.*

Table 12. Summary of key word search on the Journal of Medicinal Chemistry between January 2000 and December 2011:

Key word	#Articles containing the key word
"rational design"	571
"rational drug design"	187
“SAR”	3726
“QSAR”	745
“structure based drug design”	347
"molecular modeling"	2127
"X-ray"	3219
“docking”	2145
"homology model"	484
“drug”	6778
“compound”	8314
“molecule”	5494

As shown in the table, a significant percentage of those relevant articles (defined as those hitting one of the baseline key words), mentioned the technology used to predict properties of chemical compounds. It is fair to conclude that these predictive technologies are firmly rooted in the knowledge of people having ordinary skill in the art and are often applied in their research. Are properties of chemical compounds predictable or unpredictable? The answer may depend on both the type of the compound and the type of the property. While scientists working in the field are embracing technologies that can predict properties of chemical compounds, perhaps, the court should do the same, especially when it is possible to estimate the predictability of chemical compounds.

VII. CONCLUSION

The lead compound theory established in the 1990s, and reaffirmed after *KSR*, is the prevailing law for patent validity analysis based on obviousness for chemical compounds. As exhibited by recent decisions in the CAFC, a prima facie case of obviousness for a compound claim could be established by structural similarity between the claimed compound and the compound(s) in the prior art, if the prior art gave reason or motivation for a person having ordinary skill in the art to make the claimed compound. This is a very high standard, which has not been met by any CAFC case challenging the validity of a compound claim. Structural similarity alone does not suffice, according to the CAFC, because the court assumed that properties of

chemical compounds are unpredictable and that similar structures do not always lead to similar properties.

Recent progress in chemistry, especially in medicinal chemistry, demonstrates that certain properties of chemical compounds can be predicted. Some properties can be calculated based on fundamental physical chemical principles and other properties can be predicted through SARs and QSARs. While some properties are difficult to predict accurately, based on a reliable SAR, one can narrow the scope to a finite number of possible solutions among which the best compound can be identified through an exhaustive search. While not all compounds with similar structures have similar properties, some of them do. Cross-validation methods are available to identify compounds and properties for which reliable predictions can be made. Therefore, at least for those compounds, if the claimed utility can be directly derived from those predictable properties, it may be plausible to argue that the prima facie case of obviousness can be established based on the structural similarity between the prior art compound and the claimed compound because the predicted properties could be used to support the reason and motivation required in the lead compound theory.