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Lead Compound Analysis for Chemicals: Obvious or Nonobvious?

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I. INTRODUCTION

Baraclude®, a hepatitis B drug marked by Bristol-Myers Squibb Co. (BMS), has an active ingredient of a chemical compound, entecavir.[1] Entecavir is composed of two regions: a carbocyclic ring and a guanine base, and it is covered by a patent owned by BMS.[2] Teva Pharmaceuticals USA, Inc. (Teva) challenged the patent's validity during an infringement litigation brought by BMS.[3] Teva presented a known compound 2'-CDG and claimed entecavir was obvious over 2'-CDG.[4] Entecavir and 2'-CDG are structurally similar, the only difference being a carbon-carbon double bond (an exocyclic methylene group) at the 5' position of the carbocyclic ring in entecavir.[5] Teva contended a person having ordinary skill in the art (PHOSITA) would have been motivated to select 2'-CDG as a lead compound for further development and would have been motivated to modify the lead compound to arrive at the claimed compound, so entecavir was obvious and unpatentable.[6]

This case is an illustration of the application of the Lead Compound Analysis (LCA) in the determination of patentability of new chemical compounds on obviousness ground, especially chemical compounds in pharmaceutical patents. The LCA was established by the U.S. Court of Appeals for the Federal Circuit (Federal Circuit) in 2000 and has been applied by courts and the United State Patent and Trademark Office (USPTO) since then. Its continued application after the United State Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.*[7] has been

[1] *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 969 (Fed. Cir. 2014)
[2] *Id.*
[3] *Id.* at 970.
[4] *Id.*
[5] *Id.* at 969-70.
[6] *Id.* at 970. *See* also *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 613 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014).
[7] 550 U.S. 398 (2007).

criticized widely as rigid and inconsistent with the KSR rationale.[8] This article explains the doctrine of Lead Compound Analysis and its application in the termination of obviousness of new chemical compounds in court litigations and USPTO proceedings, and argues that the LCA is proper and consistent with the rationale under the *KSR.* Part II provides the background of the drug discovery process and emphasizes the high intellectual requirement during modern drug discovery. Part III explains the general obviousness standard under the statute and the Supreme Court decisions and summarizes the historical development of the obviousness standard in chemical art. Part IV discusses the doctrine of LCA and its application in court litigations and the USPTO proceedings, and analyzes the difference of its application between courts and USPTO proceedings. Part V argues the LCA is determined by the drug discovery process and is consistent with the *KSR* rationale. Part VI concludes the analysis on the LCA.

II. Development of Drug Discovery

Drug discovery traditionally was based on the nature's bounty and imagination of chemists. After a serendipitous biological finding, scientists engaged in serial purification of the crude extracts to obtain the active principle.[9] These compounds had unknown target and their mechanism of action were usually unknown. They were further modified to obtain simpler and more bioavailable compounds based on the core structure of the active compounds.[10] The discovery and development of Penicillin and related antibiotics is an example of such serendipitous discovery and development. Penicillin was discovered in 1929 as a metabolite

[8] Briana Barron, *Structural Uncertainty: Understanding the Federal Circuit's Lead Compound Analysis*, 16 Marq. Intell. Prop. L. Rev. 401, 403 (2012); Vincent L. Capuano, *Obviousness of Chemical Compounds: The "Lead Compound" Concept*, Intell. Prop. Today July 2007, at 33.
[9] Leland J. Gershell, Joshua H. Atkins, *A brief history of novel drug discovery technologies*, 2 Nature Revs. Drug Discovery 321 (2003), http://www.nature.com/nrd/journal/v2/n4/pdf/nrd1064.pdf.
[10] *Id.*

from a penicillium mold by Alexander Fleming when he was sorting through petri dishes containing bacteria that caused boils, sore throats and abscesses, and noticed something unusual on one dish.[11] Then in 1938, Howard Florey, Ernst Chain and their colleagues chose penicillin for further study.[12] After time-consuming extraction, purification, trial and production, penicillin became the most widely used antibiotic.[13] It opened the door to the discovery of other antibiotics and started a new era of bacterial infection treatment.[14]

With the development of chemistry, pharmacology, microbiology, and biochemistry, drug discovery became target oriented, and the understanding of biological structure and function leads to the creation of novel chemical structures suitable as drugs.[15] The modern drug discovery is a complicated process. It starts with the identification of a disease relevant target, which can be proteins, genes, or RNA.[16] "A 'druggable' target is accessible to the putative drug molecule, be that a small molecule or larger biologicals and upon binding, elicit a biological response which may be measured both *in vitro* and *in vivo*."[17] Available biomedical data is useful in the target identification.[18] This target is further validated through antisense technology, chemical genomics or other technologies.[19] Following the target identification and validation is

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[11] *The discovery and development of penicillin 1928-1945*, commemorative booklet produced by the National Historic Chemical Landmarks program of the American Chemical Society in 1999 (PDF), https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html.
[12] Jürgen Drews, *Drug Discovery: A historical Perspective*, 287 Science1960, 1960 (Mar. 17, 2000), http://science.sciencemag.org/content/287/5460/1960.full.
[13] *Supra* note 11.
[14] *Supra* note 12.
[15] *Id.*
[16] JP Hughes, S Rees, SB Kalindjian, and KL Philpott, *Principles of early drug discovery*, 162 Brit. J Pharmacology 1239, 1239 (2011 Mar), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058157/.
[17] *Id.*
[18] *Id.* at 1240.
[19] *Id.* at 1240-42.

the hit identification and lead discovery phase of the drug discovery.[20] High throughput screening (HTS) was developed to identify molecules that elicit a positive response with the drug target.[21] It involves the screening of large numbers of compounds against the drug target in various assay systems such as biochemical assays or cell-based assays.[22] These compounds represent "numerous variations on a few chemical themes or… fewer variations on a greater number of themes in high-throughput configurations."[23] Numerous data are developed for potency, selectivity and other properties of compounds, and chemistry programs are employed to improve the properties to support the hypothesis that intervention at the drug target will lead to the effective treatment of the disease.[24]

Once a number of hits are obtained, further analysis, screening, and various assays are carried out to narrow the number of hits to produce lead compounds.[25] In addition to properties like potency and selectivity, absorption, distribution, metabolism and excretion (ADME) properties as well as physicochemical and pharmacokinetic (PK) data are collected to help refine the hits.[26] During the process, the compounds may be modified to yield more potent and selective leads with desirable PK properties.[27] The lead compounds are then further optimized to achieve the favorable properties while improving on deficiencies in the lead structures.[28]

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[20] *Id.* at 1242.
[21] *Id.*
[22] *Id.* at 1242-43.
[23] Drews, *supra* note 12, at 1962.
[24] Hughes, *supra* note 16, at 1242.
[25] *Id.* at 1245-48.
[26] *Id.* at 1246.
[27] *Id.* at 1246-48.
[28] *Id.* at 1248.

The whole process of screening to lead generation and optimization is a series of time-consuming and intellectually intense activities within the pharmaceutical industry.[29] Typically, each project starts with 200,000 to >1,000,000 compounds to be screened, and the number is reduced to 100's and then down to one or two candidates, following hit-to-lead and lead optimization process.[30] "There are rarely any short cuts and significant, intellectual input is required from scientists from a variety of disciplines and backgrounds. The quality of the hit-to-lead starting point and the expertise of the available team are the key determinants of a successful outcome of this phase of work."[31]

III. Obviousness Standard and Its Historical Development in Chemical Art

Under the U.S. patent law, to be patentable, a claimed invention has to be a process, machine, manufacture, or composition of matter that is useful, novel and nonobvious.[32] The Supreme Court has interpreted the statute and set forth the standard for obviousness determination for all cases. The obviousness standard in chemical art has been focused on the structural similarity of chemicals.

A. The Foundation of the Obviousness Standard

The general obviousness standard applicable to all patents are set forth in the statute and the U.S. Supreme Court decisions in *Graham v. John Deere Co. of Kansas City*[33] and *KSR Int'l Co. v. Teleflex Inc.*[34]

Under 35 U.S.C. § 103, a claimed invention is obvious "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have

[29] *Id.* at 1242, 1248.
[30] *Id.* at 1248.
[31] *Id.*
[32] 35 U.S.C. § 102-103.
[33] 383 U.S. 1 (1966).
[34] 550 U.S. 398 (2007).

been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art."[35] The U.S. Supreme Court examined the statute and laid out the standard for the obviousness determination in *Graham*.[36] The obviousness of a subject matter should be assessed according to the scope and content of the prior art, the difference between the prior art and the claimed invention, the level of the ordinary skill in the art, any secondary considerations such as commercial success, long felt but unsolved needs, and failure of others.[37]

To implement this obviousness standard, the Federal Circuit had developed a teaching, suggestion, or motivation (TSM) test.[38] Under this test, there has to be some teaching, motivation or suggestion in the prior art itself, the nature of the problem or knowledge of a PHOSITA to combine the elements of prior art to render the claimed invention obvious.[39] The TSM provided some certainty and predictability in the lower courts in applying the obviousness standard set forth by the Supreme Court.[40] It was also criticized as imposing a higher standard on patent challengers and being inconsistent with section 103 or *Graham*.[41]

In 2007, the Supreme Court decided *KSR Int'l Co. v. Teleflex Inc.*, and rejected Federal Circuit's TSM test as the exclusive test for obviousness.[42] In *KSR*, Teleflex Inc. (Teleflex) was the exclusive licensee of a patent claiming an adjustable electronic pedal assembly with an electronic pedal position sensor attached to a fixed pivot point of the assembly for vehicles.[43] Teleflex sued KSR International Company (KSR) for infringement of this patent after KSR

[35] 35 U.S.C. § 103.
[36] 383 U.S. at 13-18.
[37] *Id.* at 17.
[38] *KSR*, 550 U.S. at 399.
[39] *Id.*
[40] James Skelley, *Teaching-Suggestion-Motivation Under Review: Developments in KRS International Co. v. Teleflex, Inc.*, 13 B.U. J. Sci. & Tech. L. 107, 118 (2007).
[41] *Id.* at 110, 114-117.
[42] 550 U.S. at 415.
[43] *Id.* at 410-11.

combined an adjustable pedal system with electronic throttle control.[44] KSR countered that the patent claim was invalid for obviousness.[45] The district court granted KSR's summary judgment on the ground of obviousness because the prior art taught every element of the claim and the prior art and the state of the industry provided suggestion or motivation to combine the elements.[46] The Federal Circuit reversed and ruled the district court did not apply the TSM test strict enough.[47] The Federal Circuit found the prior art did not address the exact problem the patentee was trying to solve, and there was not sufficient motivation or suggestion for a PHOSITA to combine the electronic sensor on the adjustable pedal system.[48]

The Supreme Court reversed and held the combination of the existing elements was a design step well within a PHOSITA's knowledge and the benefit of doing so was obvious.[49] The Court found such a combination of existing elements according to known methods yielded predictable benefits, and the marketplace would have incentivized a PHOSITA to make such combination.[50] The Court opined that interrelated teachings of prior art references, demands known to the design community or the marketplace, any need or problem know in the field and addressed by the patent, and the background knowledge of a PHOSITA were necessary in determining whether there was a reason or motivation to combine the known elements.[51] Common sense could also direct a PHOSITA to look beyond the primary purpose of familiar items and fit prior art teachings together.[52] In addition, if "there is a design need or market

[44] *Id.*
[45] *Id.* at 405.
[46] *Id.* at 412-13.
[47] *Id.* at 413-14.
[48] *Id.* at 414.
[49] *Id.* at 427-28.
[50] *Id.* at 422-25.
[51] *Id.* at 418, 420.
[52] *Id.* at 420.

pressure to solve a problem and there are a finite number of identified, predictable solutions," it is obvious for a PHOSITA to try the combination, and "[i]f this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."[53] The *KSR* decision returned the obviousness analysis to a flexible approach.

B. Historical Development of the Obviousness Doctrines in Chemical Art

In the determination of patentability under obviousness ground, the procedural mechanism includes the establishment of a *prima facie* obviousness. A patent examiner, or in the case a party who challenges the patented claim for obviousness, has the initial burden to establish any *prima facie* conclusion of obviousness.[54] If the examiner or the party establishes such case, the burden shifts to the patent applicant or owner to rebut the obviousness showing.[55] The rebuttal evidence includes "comparative test data showing that the claimed invention possesses improved properties not expected by the prior art."[56] Early cases involving obviousness of new chemical compounds focused on the standard of the *prima facie* obviousness. Under the third *Graham* factor, *prima facie* obviousness "generally turns on the structural similarities and differences between the claimed compound and the prior art compounds."[57]

The early doctrine of obviousness for chemical compounds was set forth in the "Haas-Henze" cases, decisions by the U.S. Court of Customs and Patent Appeals (CCPA) in *In re Haas*

[53] *Id.* at 421.
[54] 2142 Legal Concept of Prima Facie Obviousness (R-07.2015), MPEP s 2142; § 9:74.Generally—Properties of chemical compositions—prima facie, or structural obviousness, 3 Moy's Walker on Patents § 9:74 (4th ed.).
[55] 2142 Legal Concept of Prima Facie Obviousness (R-07.2015), MPEP s 2142
[56] *Id.*
[57] *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012) (Citing *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed.Cir.2010).

and *In re Henze*.[58] Under the "Haas-Henze" doctrine, if a claimed chemical compound is structurally similar to a prior art compound, there is a presumption of obviousness (older term of *prima facie* obviousness) because of the assumption that structurally similar compounds have similar properties.[59] This presumption could be rebutted "by a showing that the claimed compound possesses unobvious or unexpected beneficial properties not actually possessed by the prior art" compound.[60] This doctrine was later overruled and a new standard was announced in *In re Dillon.*[61]

In *In re Dillon*, Dillon's patent application related to hydrocarbon fuel compositions containing certain tetra-orthoesters, and the patent application disclosed that the compositions were useful in reducing the emission of solid particulates during combustion of the fuel.[62] The USPTO rejected all the claims directed to the compositions and method for obviousness over three prior art patents, U.S. Patent Number 4,390,417 ('417 patent), 4,395,267 ('267 patent), and 3,903,006 ('006 patent).[63] The '417 patent disclosed hydrocarbon fuel compositions containing chemical compounds including tri-orthoesters, useful for dewatering fuels.[64] The '267 patent described hydrocarbon fuel composition containing alcohol immiscible with the fuel, and tri-orthoesters.[65] The tri-orthoester serves as a cosolvent to make the whole composition a single phase.[66] The '006 patent disclosed and suggested that tri-orthoesters and tetra-orthoesters were

[58] *In re Hass*, 141 F.2d 122, 124 (C.C.P.A. 1944); *Application of Henze*, 181 F.2d 196 (C.C.P.A. 1950) overruled by *Application of Stemniski*, 444 F.2d 581 (C.C.P.A. 1971).
[59] *See* Guttag, *The Hass-Henze Doctrine*, 43 JPOS 808 (1961).
[60] *Henze*, 181 F.2d at 201.
[61] 919 F.2d 688 (Fed. Cir. 1990).
[62] *Id.* at 690.
[63] *Id.* at 691.
[64] *Id.*
[65] *Id.*
[66] *Id.*

equivalent in their use to remove water from hydraulic fluids.[67] However, none of the prior art disclosed the combination of hydrocarbon fuel with tetra-orthoester and their use in reducing particulate emissions recited in Dillon's patent application.[68]

The Federal Circuit affirmed the PTO's rejection of the claims on the obviousness ground.[69] The court found there was a close relationship between tri- and tetra-orthoesters in the fuel oil art, so there was a reasonable expectation the tri-and tetra-oethoester compositions would have similar properties.[70] This would have created sufficient motivation for a PHOSITA to make a new composition containing tetra-orthoesters.[71] Therefore, a *prima facie* case of obviousness had been made.[72] Although the new use was not described or suggested in any prior art, this did not defeat the *prima facie* case, and the composition claims were not limited to the new use.[73] Unless Dillon could rebut the *prima facie* case of obviousness with some unexpected advantage or properties, the claims were unpatentable for obviousness.[74]

Therefore, the *Dillon* court formulated the new standard of *prima facie* obviousness for chemical art. Under the standard, a chemical compound or composition is *prima facie* obvious if the compound or composition is structurally similar to the prior art, and the art provides any reason or motivation to make the claimed compound or composition.[75] The *prima facie* obviousness can be rebutted by unexpected properties not present in the prior art, by no

[67] *Id.*
[68] *Id.*
[69] *Id.* at 695.
[70] *Id.* at 692.
[71] *Id.*
[72] *Id.* at 693.
[73] *Id.* at 692-93.
[74] *Id.*
[75] *Id.* at 692.

motivation in the prior art, or by other relevant argument.[76] The *Dillon* court specifically rejected the requirement that the prior art provides some suggestion or expectation that the new compound or composition has the *same or a similar utility*.[77] Under the *Dillon* standard, any motivation that suggests modification of the prior art compound or composition into the claimed invention would be sufficient for a *prima facie* showing of structural obviousness.[78] The Dillon *prima facie* obviousness standard is still good law and is still applied by courts and the USPTO.

IV. Lead Compound Analysis

The Lead Compound Analysis was established by the Federal Circuit in 2000 in *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc*.[79] It has been used for the determination of whether a new chemical compound would have been *prima facie* obvious over prior art compounds by courts since then, especially new chemical compounds in pharmaceutical patents. The USPTO has also applied the LCA in various proceedings.

The "lead compound" in the LCA is defined as "a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity,"[80] and it is "a natural choice for further development efforts."[81] The analysis follows a two-step inquiry.[82] First, the court determines whether a PHOSITA would have selected the prior art compounds as lead compounds for further development.[83] Second, the court determines whether some reason or motivation would have prompted the PHOSITA to modify

[76] *Id.*
[77] *Id.*
[78] § 9:74.Generally—Properties of chemical compositions—prima facie, or structural obviousness, 3 Moy's Walker on Patents § 9:74 (4th ed.).
[79] 231 F.3d 1339 (Fed. Cir. 2000).
[80] *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd*., 492 F.3d 1350, 1357 (Fed. Cir. 2007)
[81] *Altana Pharma AG v. Teva Pharms. USA, Inc*., 566 F.3d 999, 1008 (Fed. Cir. 2009).
[82] *Otsuka*, 678 F.3d at 1291.
[83] *Id.*

the lead compounds to make the claimed compounds with a reasonable expectation of success.[84]

A. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.

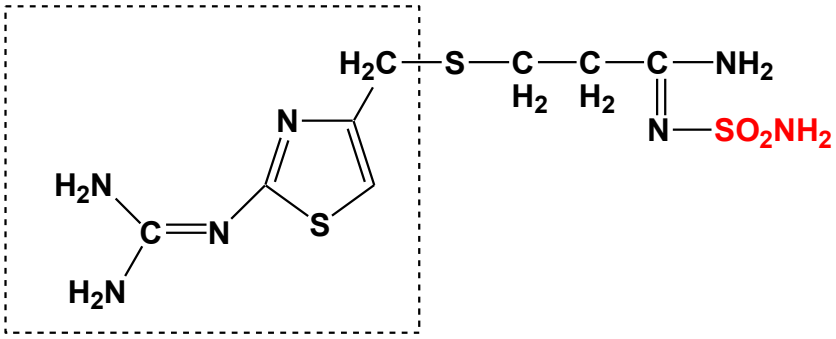
The chemical compound at issue in *Yamanouchi* is famotidine (see structure below), for treating heartburn and ulcers.[85] It belongs to a class of inhibitors of stomach acid secretion.[86] Yamanouchi Pharmaceutical Co., Ltd. and Merck & Co., Inc. (Yamanouchi) owned a U.S. Patent No. 4,283,408 ('408 patent) claiming famotidine for treating heartburn and ulcers.[87] Danbury Pharmacal, Inc. (Danbury) filed an Abbreviated New Drug Application (ANDA) with the Food and Drug Administration (FDA) for approval of making generic famotidine.[88] The application also included a paragraph IV certification, which inserted the patent was invalid or would not be infringed by the drug for which the approval was sought.[89] Under the Drug Price Competition and Patent Term Restoration Act, also known as the Hatch–Waxman Act, the filing of a paragraph IV certification is treated as a technical act of patent infringement.[90] Yamanouchi then filed suit against Danbury for patent infringement under 35 U.S.C. § 271(e)(2)(A).[91] The district court ruled that Danbury did not show by clear and convincing evidence that the '408 patent was obvious at the time of the invention.[92]

On appeal, the Federal Circuit affirmed.[93] It first examined the history of the development of this drug, and noted that out of 11,000 compound candidates of this class of compounds synthesized by pharmaceutical companies, four were eventually approved by the

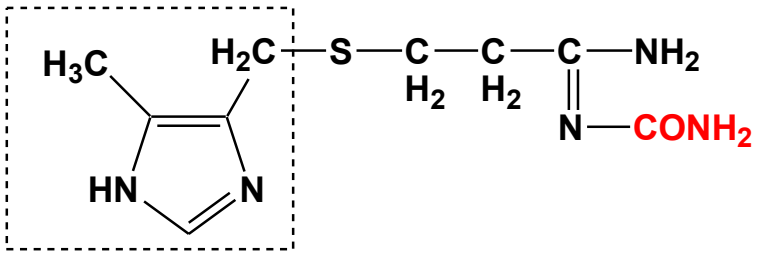
[84] *Id.* at 1292.
[85] 231 F.3d at 1341.
[86] *Id.*
[87] *Id.*
[88] *Id.* at 1342.
[89] *Id.*
[90] 21 U.S.C. § 271(e)(2).
[91] *Yamanouchi*, 231 F.3d at 1342.
[92] *Id.*
[93] *Id.* at 1348.

FDA.[94] The Federal Circuit then examined the prior art compounds Danbury presented for its obviousness argument.[95] Danbury argued one of ordinary skill in the art would consider it obvious to select the example 44 from a prior art patent as a lead compound, and replace the left side ring with the ring structure from tiotidine, a known failed compound in the 11,000 candidates, and finally substitute the CONH group in example 44 with a SO_2NH_2 group to create famotidine.[96]

Famotidine:

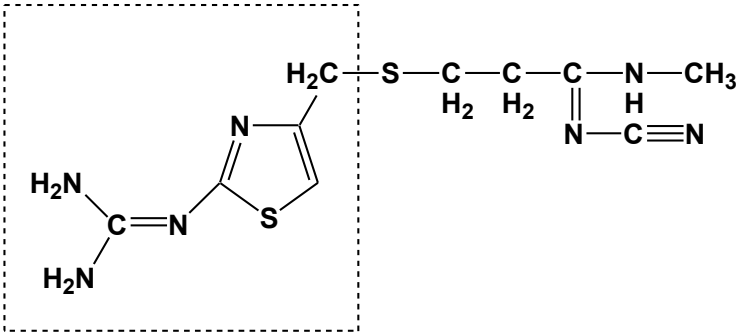


Example 44:



[94] *Id.* at 1341-42.
[95] *Id.* at 1343-45.
[96] *Id.*

Tiotidine:



The Federal Circuit found there was no motivation for a person of skill in the art to select the prior art compounds Danbury presented.[97] The fact that Example 44 was three times more active than cimetidine (a benchmark compound at the time of invention) was not a sufficient motivation, since other prior art references disclosed compounds with activities of ten times higher than cimetidine.[98] Therefore, Example 44 was not an obvious choice.[99]

The Federal Circuit also found there was no motivation to replace the left side ring in example 44 with the ring structure from tiotidine and then substitute the CONH2 group because there was no reasonable expectation of success.[100] An expected baseline level of activity, which is a merely 1/165th the activity of cimetidine, was not a motivation for a reasonable expectation of success.[101] The reasonable expectation required finding a compound with high activity, few side effects, and lacked toxicity.[102]

[97] *Id.* at 1345.
[98] *Id.*
[99] *Id.*
[100] *Id.*
[101] *Id.*
[102] *Id.*

The court also noted there was no motivation for a person of ordinary skill to pursue the precise steps required to achieve the invention.[103] A slight change of order of the steps would result in a compound of much reduced activity, resulting teaching away from famotidine.[104] Therefore, it would not have been obvious to follow the specific steps to arrive at the invention.[105]

B. Lead Compound Analysis in Courts Litigations

The application of LCA in court litigations has been focused on the determination of obviousness of chemical compounds in pharmaceutical patents. The reason or motivation for a PHOSITA to select a prior art compound as the lead compound is critical in the determination.

1. Motivation to Select

In applying the first prong of the LAC, the Federal Circuit has considered various factors to determine whether a PHOSITA would have selected a prior art compound as the lead compound.

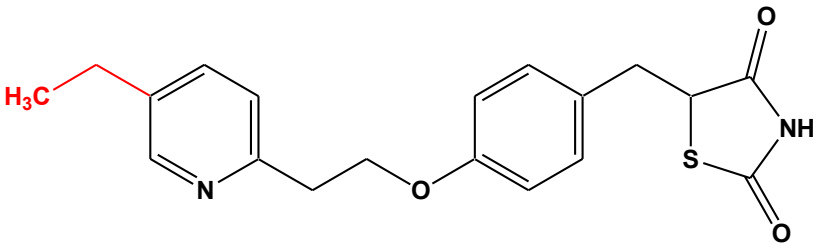
i. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.

In *Takeda*, the Federal Circuit found a structurally close prior compound would not be considered by a PHOSITA as a lead compound because of its adverse effect.[106] In this case, Takeda Chemical Industries, LTD and Takeda Pharmaceuticals North America, Inc. (Takeda) developed the drug ACTOS® for Type 2 diabetes, which contained the active ingredient pioglitazone.[107] This chemical compound was covered in the U.S. Patent 4,687,777 (the "′777 patent"), directed to "antidiabetic agents having a broad safety margin between pharmacological

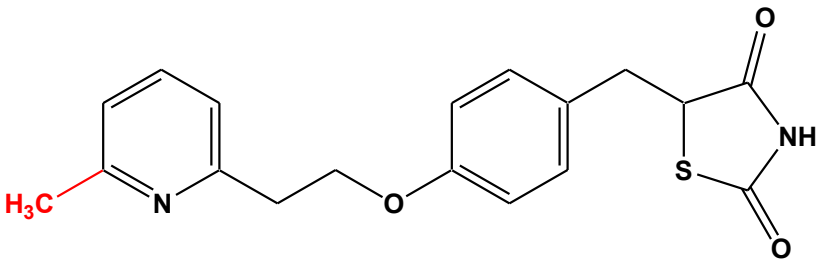
[103] *Id.*
[104] *Id.*
[105] *Id.*
[106] 492 F.3d at 1360.
[107] *Id.* at 1352-53.

effect and toxicity or unfavorable side reactions."[108] Alphapharm Pty., Ltd. (Alphapharm) filed an ANDA and challenged the validity of the patent for obviousness over a prior art compound, compound b.[109] Alphapharm asserted compound b was structurally similar to pioglitazone and was the most effective antidiabetic compound in the prior art at the time of the invention, so a PHOSITA would have selected compound b as the lead compound.[110] The district court found there was no motivation to select compound b as the lead compound and the prior art taught away from its use as antidiabetic agent.[111]

Pioglitazone:



Compound b:



[108] *Id.* at 1353 (citing '777 patent col.1 ll.34–37).
[109] *Id.* at 1354.
[110] *Id.* at 1355.
[111] *Id.* at 1354.

The Federal circuit agreed and noted the prior art patent (‘200 patent) disclosed hundreds of millions of compounds, including compound b.[112] Although ‘200 patent specifically identified fifty-four compounds synthesized, it did not disclose any experimental data or test results.[113] The prosecution history of the ‘200 patent revealed test results of compound b along with other eight compounds, but the court noted the information was provided in response to a rejection to show compounds in ‘200 patent were superior over known compounds.[114] The court therefore found there was no suggestion to a PHOSITA that the nine compounds in the prosecution history were best candidates for antidiabetic research. Further, the court noted another prior art article disclosed hypoglycemic activity of 101 compounds, including compound b.[115] The article specifically identified three compounds as most favorable compounds, and compound b was not one of them.[116] Instead, the article singled out compound b as causing “considerable increase in body weight and brown fat weight.”[117] The court thus believed that the negative properties would have directed a PHOSITA away from selecting compound b as the lead compound.[118]

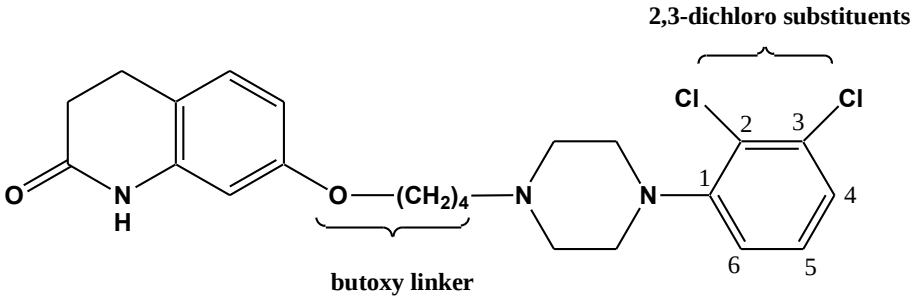
ii. Otsuka Pharm. Co. v. Sandoz, Inc.

In *Otsuka*, the Federal Circuit stressed the importance of a compound’s pertinent property in guiding a PHOSITA to select a lead compound.[119] The compound at issue is aripiprazole, the active ingredient in the antipsychotic drug Abilify®, for the treatment of schizophrenia, bipolar disorder, irritability associated with autistic disorder in pediatric patients. [120] ANDA filers

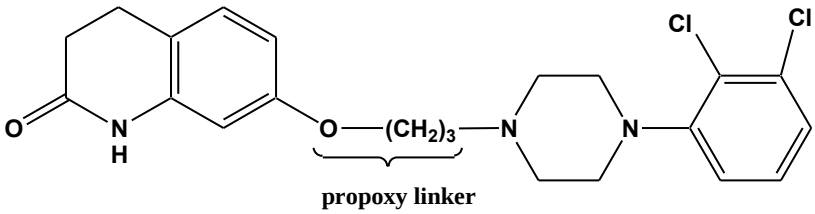
[112] *Id.* at 1357.
[113] *Id.*
[114] *Id.*
[115] *Id.* at 1358.
[116] *Id.*
[117] *Id.*
[118] *Id.* at 1358-60.
[119] 678 F.3d at 1292.
[120] *Id.* at 1284.

challenged the patent covering aripiprazole for obviousness over three prior art compounds, unsubstituted butoxy, 2,3-dichloro propoxy, and OPC-4392.[121] The three compounds are all structurally similar to aripiprazole. However, the unsubstituted butoxy lacks the 2,3-dichloro substituent on the pheny ring; the 2,3-dichloro propoxy has a propoxy linker instead of a butoxy linker; and the OPC-4392 is different on the 3,4-dihydrocarbostyril ring and the substituents on the phenyl ring (see structures below). The Federal Circuit examined the properties of the prior art compounds, and affirmed the district court that the ANDA filers failed to prove by clear and convincing evidence that a PHOSITA would have selected these compounds as lead compounds for their obviousness claim.[122]

Aripiprazole:

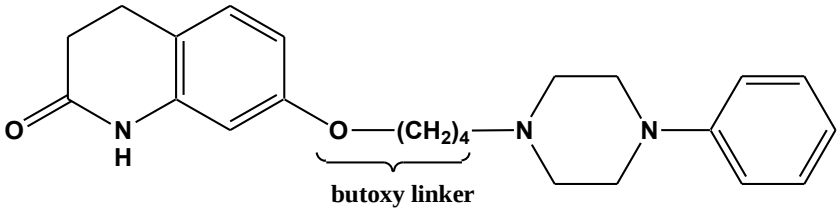


"2,3-Dichloro propoxy":

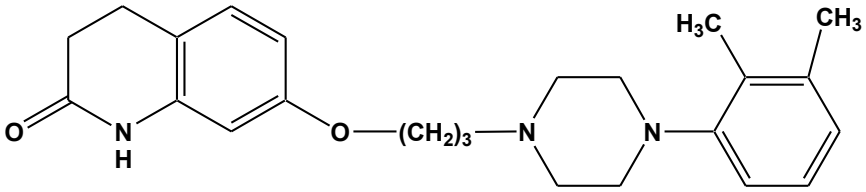


[121] *Id.* at 1285-89.
[122] *Id.* at 1291-96.

"Unsubstituted butoxy":



OPC-4392:



For the 2,3-dichloro propoxy, the Federal Circuit noted this compound was buried in hundreds of examples that might be useful for central nervous system controlling properties, and the prior art did not provide motivation to narrow the examples to the 2,3-dichloro propoxy compound.[123] The court rejected the argument that a generic disclosure is enough for obviousness.[124]

For the unsubstituted butoxy compound, the Federal Circuit noted it was among nine trillion compounds claimed in the prior art, with a "laundry list" of potential central nervous system controlling properties.[125] Although there was some mouse jumping test data on the unsubstituted butoxy compound, along with other ten compounds,[126] the data showed four

[123] *Id.* at 1295.
[124] *Id.*
[125] *Id.* at 1286, 1294.
[126] *Id.* at 1287. The test data was disclosed in a declaration submitted during the prosecution of the patent. The district court found a PHOSITA could consider the mouse jumping data to be indicative of antipsychotic activity.

compounds had greater potency than the unsubstituted butoxy compound, and all four compounds had a propoxy linker, with one compound being ten times more potent than the unsubstituted butoxy compound.[127]

The court also rejected the OPC-4392 as a lead compound because the prior art taught away from selecting OPC-4392 as a lead compound.[128] Although a prior art reference stated OPC-4392 was an antipsychotic drug, and OPC-4392 proceeded to the Phase II clinic trials, the same reference also stated the activity was not strong, and the drug was likely to cause patients to act out on their delusions and hallucinations.[129] Other references cautioned on the sever side effects of OPC-4392 in low doses.[130] Therefore, based on the totality of the prior art, OPC-4392 would not have been selected as a lead compound.[131]

In emphasizing "'[p]otent and promising activity in the prior art trumps mere structural relationships,'" the Federal Circuit concluded that ANDA filers failed to prove aripiprazole would have been obvious over the asserted prior art compounds, and their obviousness argument was based on impermissible hindsight reasoning.[132]

iii. Eisai Co. v. Dr. Reddy's Labs., Ltd.

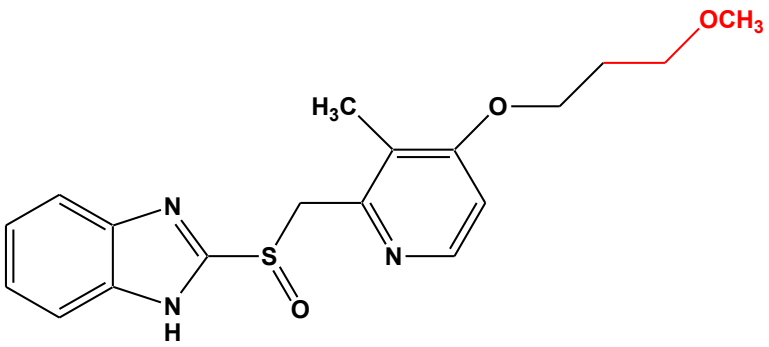
In *Eisai*, the compound at issue belonged to a class of drugs known as proton pump inhibitors that suppress gastric acid production.[133] The Omeprazole or Prilosec® is a blockbuster drug of this class for heartburn or other symptoms.[134] Eisai Co., Ltd. and Eisai, Inc. (Eisai) owned a patent claiming rabeprazole, an active ingredient in Aciphex, a drug approved by the

[127] *Id.* at 1287-88, 1293-94.
[128] *Id.* at 1295-96.
[129] *Id.*
[130] *Id.* at 1296.
[131] *Id.*
[132] *Id.* at 1293, 1296 (quoting *Daiichi*, 619 F.3d at 1354).
[133] *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008).
[134] *Altana*, 566 F.3d at 1003.

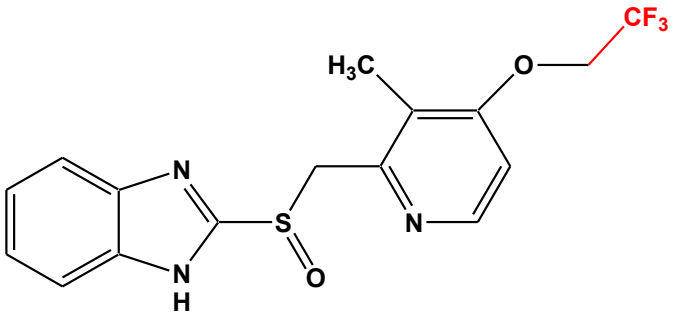
FDA for the treatment of duodenal ulcers, heartburn, and associated disorders.[135] Rabeprazole was challenged by ANDA filers as unpatentable for obviousness over a prior art compound lansoprazole.[136] Lansoprazole was disclosed in a European patent as a compound for ulcer treatment.[137] It is structurally identical to rabeprazole, except at the 4-position on the pyridine ring, lansoprazole has a trifluoroethoxy (OCH_2CF_3) substituent, while rabeprazole has a methoxypropoxy ($OCH_2CH_2CH_2$ OCH_3) substituent (see structure below).[138] The district court found a PHOSITA would not have selected lansoprazole as a lead compound in the search for antiulcer compounds.[139] Although lansoprazole's anti-ulcer activity is twenty times superior to omeprazole, the district court emphasized on the difference between anti-ulcer action and gastric acid inhibition. The district court noted a PHOSITA searching for a gastric acid inhibitor would not have considered the anti-ulcer data to determine the acid inhibition activity.[140] The Federal Circuit found this distinction not dispositive in determining whether a PHOSITA would have selected lansoprazole as the lead compound.[141] Nonetheless, it agreed with the district court that because the fluorinated substitute in lansoprazole provided for enhanced lipophilicity (an advantageous property of a compound to cross lipid membrane),[142] a PHOSITA would not have been motivated to modify lansoprazole in such a way to remove the fluorinated substituent that gave the advantageous property.[143]

[135] *Eisai*, 533 F.3d at 1356.
[136] *Id.* at 1356-57.
[137] *Id.* at 1357.
[138] *Id.*
[139] *Id.* at 1358.
[140] *Id.*
[141] *Id.*
[142] *Id.*
[143] *Id.*

Rabeprazole:



Lansoprazole:



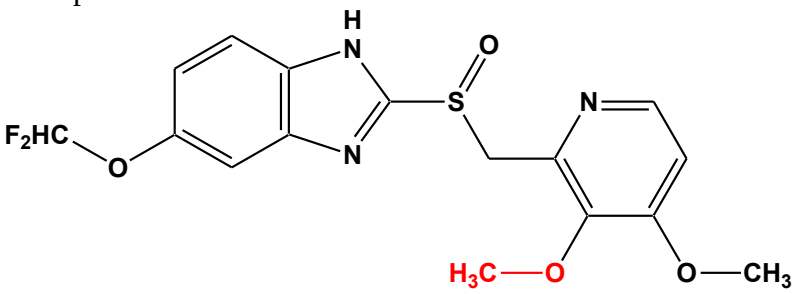
iv. Altana Pharma AG v. Teva Pharm. USA, Inc.

In *Altana*, the Federal Circuit found a PHOSITA would have been motivated to select the prior art compound as the lead compound. The chemical compound at issue belongs to a class of drugs known as proton pump inhibitors that suppress gastric acid production.[144] Omeprazole or Prilosec® is a blockbuster drug of this class for heartburn or other symptoms.[145] Altana Pharma AG and Wyeth (Altana) owned a U.S. patent No. 4,758,579 (the '579 patent) claiming pantoprazole, the active ingredient in Altana's antiulcer drug Protonix®.[146] Teva filed an ANDA for the FDA approval of a generic Protonix®, and also filed a paragraph IV certification

[144] *Altana*, 566 F.3d at 1002.
[145] *Id.* at 1003.
[146] *Id.*

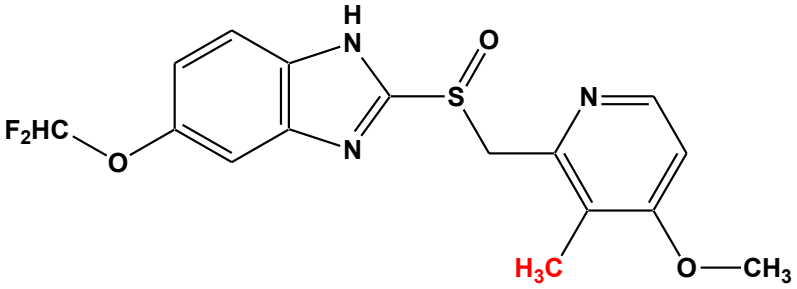
challenging the validity of the '579 patent.[147] In considering Altana's motion for preliminary injunction, the district court found Teva had raised a substantial argument that a PHOSITA would have selected a prior art compound 12 as the lead compound.[148] Compound 12 was disclosed in a U.S. Patent No. 4,555,518 ('518 patent), and the patent compared the effectiveness of eighteen claimed compounds, including compound 12, against prior art compounds of the class of proton pump inhibitors.[149] The Federal Circuit agreed with the district court that compound 12 was a natural choice for further development, and noted that the claimed compounds were improvement over the prior art, especially omeprazole.[150] In addition, compound 12 was one of the more potent of the eighteen compounds in the '518 patent with the activity data.[151]

Pantaprazole:



[147] *Id.* at 1004.
[148] *Id.* at 1007.
[149] *Id.* at 1003.
[150] *Id.* at 1007.
[151] *Id.* at 1007-08.

Compound 12:



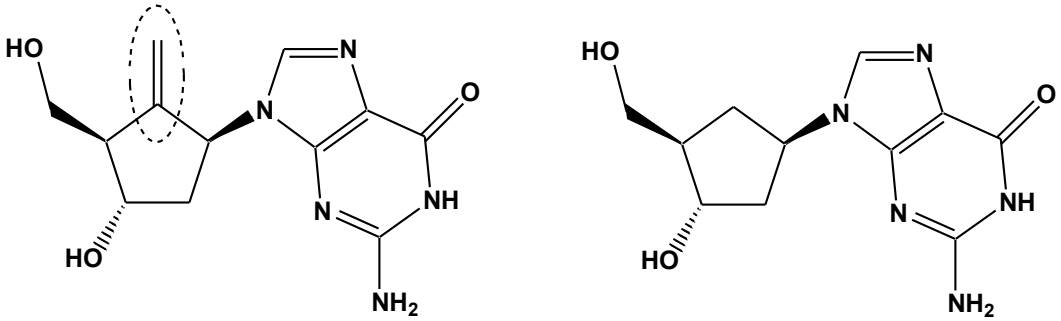
v. Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.

Similarly, in *Bristol-Myers Squibb* (*BMS*) mentioned at the beginning of this article, the court found the prior art could be considered as the lead compound. The Federal Circuit affirmed the district court decision that a PHOSITA would have selected 2'-CDG as the lead compound for further research.[152] The court examined the state of the antiviral drug discovery at the time of the invention, and noted that research on carbocyclic analogs was a focus for antiviral activity.[153] At that time, 2'-CDG generated a lot of interests among researchers from reporting on its better antiviral activity against the herpes virus than Ara-A, an FDA-approved best selling drug at that time, and its excellent activity against the hepatitis B virus.[154] Therefore, 2'-CDG was a natural choice.[155] Even though 2'-CDG was discovered to be highly toxic later, which would prevent a PHOSITA to select it as a lead compound, the court noted that at the time of the invention, the high toxicity was not yet known to the scientific community.[156] On the contrary, the prior art showed 2'-CDG was generally understood at the time of the invention to be safe and nontoxic.[157] Because the perspective of a PHOSITA at the time of the invention was the relevant

[152] *Bristol-Myers Squibb*, 752 F.3d at 973.
[153] *Id.* at 974.
[154] *Id.* at 971.
[155] *Id.* at 975.
[156] *Id.*
[157] *Id.*

consideration,[158] the PHOSITA would have been motivated to select 2'-CDG as the lead compound for further development.[159]

Entacavir: 2'-CDG:



After the court determines that a PHOSITA would have been motivated to select the prior art compound as the lead compound, it then examines whether the PHOSITA would have been motivated to modify the lead compound to make the claimed new compound.

2. Motivation to Modify

In *Altana*, the district court found there was a motivation to modify the prior art compound 12 in the prior art to arrive at the claimed invention.[160] One prior art taught a p*K*a value[161] of four would be desirable for an effective PPI because of a better stability of the compound in the body.[162] Another prior art article disclosed p*K*a values of different compounds, and taught a lower p*K*a value would be resulted from a methoxy group (-OCH_3) at the 3-position of the pyridine ring than from a methy group (-CH_3) at the same position.[163] The Federal Circuit affirmed the district court decision and found the first prior art motivated a PHOSITA to modify

[158] For patents filed under the America Invents Act (AIA), the relevant consideration is based on the time of the filing.
[159] *Bristol-Myers Squibb*, 752 F.3d at 975.
[160] *Altana*, 566 F.3d at 1009-10.
[161] *Id.*at 1004. The p*K*a value "indicates the degree of the willingness of the compound to accept or donate a proton."
[162] *Id.*at 1009.
[163] *Id.*

the prior art compounds to reduce p*K*a values to 4, and the second prior art provided the specific teaching to reduce the p*K*a value in the direction leading to the claimed compound.[164]

In *Takeda*, the court found a PHOSITA would not be motivated to modify compound b to achieve the claim invention.[165] To make pioglitazone from compound b, a PHOSITA would have to replace the methyl group with an ethyl group on the pyridyl ring, and then move the ethyl group from the 6-position to the 5-position.[166] The court found nothing in the prior art suggested such specific modifications and the process was not routine at the time of the invention.[167] Since there were wide choices of substituents on the pyridyl ring, such as chloride, fluoride or others, a PHOSITA would not be motivated to select a methyl group.[168] Based on the prior art article teaching, adding a methyl group would not decrease unwanted side effects, so the court found there was no reasonable expectation that the methyl group would enhance its property in body weight and brown fat weight.[169] Due to the lack of the reasonable expectation of success, the court concluded that a PHOSITA would not be motivated to modify compound b to make the claimed compound.[170]

In *BMS*, the court found with 2'-CDG as the lead compound, a PHOSITA would be motivated to modify its carbocyclic ring by substituting an exocyclic methylene group at the 5' position to made entecavir.[171] The expert testimony explained small changes on the 2' or 5' position of the carbocyclic ring were obvious choices to make to modify the lead compound.[172]

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[164] *Id.*at 1009-10.
[165] *Takeda*, 492 F.3d at 1360.
[166] *Id.*at 1357.
[167] *Id.*at 1360.
[168] *Id.*
[169] *Id.*
[170] *Id.*at 1362.
[171] *Bristol-Myers Squibb*, 752 F.3d at 975.
[172] *Id.*

Prior art references also disclosed that exocyclic methylene substitution at the 5' position on the carbocyclic ring of a structurally similar compound led to superior antiviral properties.[173] Therefore, in light of the prior art and a PHOSITA's knowledge, it was obvious to modify 2'-CDG to make the claimed compound, and the modification was from a small and finite number of changes to try to get to the invention.[174] Since structurally similar compounds generally have similar properties, a PHOSITA would have a reasonable expectation of success based on the properties of prior art compounds.[175]

B. LCA in USPTO Proceedings

The USPTO proceedings provide mechanisms for parties to appeal Patent Examiner's adverse decisions in patent applications and reexamination proceedings, and to challenge the patentability of issued patents.[176] The Patent Trial and Appeal Board (PTAB) is the administrative law body of the USPTO,[177] and it has applied the LCA in the proceedings.

1. USPTO Proceedings

The proceedings at the Patent Office include *ex parte* appeal to the PTAB[178], *ex parte* Reexamination (EPR), Post Grant Review (PGR), Inter Partes Review (IPR), Transitional Program for Covered Business Method Patents, Derivation Proceeding[179] and other proceedings.

In an *ex parte* appeal, a patent applicant or owner appeals to the PTAB Patent Examiner's final rejection of a patent application or patent in a reexamination.[180] The appellant can

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[173] *Id.* at 971-72.
[174] *Id.* at 976.
[175] *Id.*
[176] Welcome to the Patent Trial and Appeal Board (PTAB), *USPTO*, https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board-0.
[177] *Id.* The PTAB was formed on September 16, 2012 as a part of the America Invents Act. It replaces the Board of Patent Appeals and Interferences (BPAI). This article only addresses the PTAB decisions.
[178] 35 U.S.C. § 134.
[179] 35 U.S.C. § 135.

overcome the examiner's rejection by preponderance of evidence that the examiner was error in the underlying finding of fact or the reasoning used to establish the *prima facie* obviousness.[181]

The EPR proceedings generally involve only the patent owner and the USPTO. Through EPR, the patent owner may request an USPTO examination of an issued patent based on prior art the owner brings to the USPTO's attention. If the owner establishes a substantial and new question of patentability (SNQ), the PTO will grant the request and order reexamination of the patent. The patent owner can appeal the final decision to the PTAB, and then to the Federal Circuit.

In PGR, a third party (a person who is not the owner of the patent) files a petition to the PTAB on or within nine months after the patent is issued or reissued.[182] If the party can show that it is more likely than not that at least on claim challenged is unpatentable, the PTAB may institute the review and make a final determination within one year.[183] The PGR generally applies to patents issued under the first-inventor-to-file provisions of the American Invents Act (AIA).[184]

In IPR, a third party files a petition to the PTAB, and in the case of first-inventor-to-file patents, the time for file is after nine months of the patent's issuance or reissuance, or after the termination of the PGR if a PGR is instituted, whichever is later.[185] For first-to-invent patents, the party can file at any time.[186] If the party can show there is a reasonable likelihood he would

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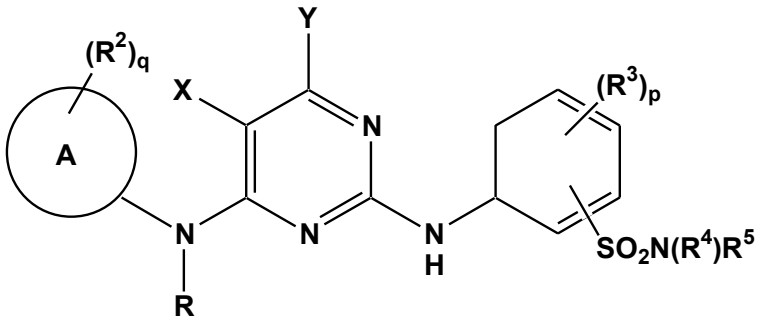
[180] 35 U.S.C. § 134.
[181] *Ex Parte Frye*, 94 U.S.P.Q.2d 1072 (P.T.O. Feb. 26, 2010).
[182] Post Grant Review, *USPTO*, https://www.uspto.gov/patents-application-process/appealing-patent-decisions/trials/post-grant-review.
[183] *Id.*
[184] *Id.*
[185] *Inter Partes* Review, *USPTO*, https://www.uspto.gov/patents-application-process/appealing-patent-decisions/trials/inter-partes-review.
[186] *Id.*

prevail with respect to the patentability of at least one claim challenged, the PTAB may institute the review and make a final determination within one year.[187] The only ground of unpatentability the party can raise is under section 102 and 103, and only on prior art that is patent or printed publications.[188]

2. The Application of LCA by PTAB

i. LCA Is Not Required in Every Chemical Case

In *Ex Parte Argade*, patent applicants appealed the Patent Examiner's rejection of patent claims to the PTAB.[189] Claim 1 of the patent at issue claims compounds as protein kinase inhibitors with the formula I:[190]



I

Claim one was rejected for obviousness because a prior art reference disclosed a generic group of compounds that encompassed the claimed compounds, and were useful as pharmaceutical therapeutic agents for the treatment disease such as cancer.[191] The Examiner found one example of a specific compound in the prior art reference was structurally similar to the claimed compounds.[192] The patent applicants contended the Examiner did not establish a *prima facie* case

[187] *Id.*
[188] *Id.*
[189] *Ex Parte Argade*, APPEAL 2013-008708, 2016 WL 4254893, at 1 (Aug. 10, 2016).
[190] *Id.*
[191] *Id.*at 8.
[192] *Id.*

of obviousness because the prior art did not expressly disclose any particular compound as a lead compound, nor provided compounds' activity or potency data for a PHOSITA to select the compound as lead compound.[193] The PTAB disposed of the argument that the Examiner has to follow the LCA in this situation, and noted that the LCA applied in the context of claims to a specific compound as in *Otsuka* and *Daiichi*.[194] In this case, claim 1 is a genus claim covering a large number of chemical compounds, so the *Dillon* analysis is more appropriate.[195] Since the prior art compounds were useful for the same purpose as the claimed compound and fell under the scope of generic claim 1, and the Examiner also identified in the prior art some motivation to modify the compounds, the PTAB concluded there was no error in Examiner's rejection of the claim for obviousness ground.[196]

The PTAB also found the LCA might not be proper for the obviousness analysis of composition claims. Composition claims are claims that "include 'all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids.'"[197]

In *Ex Parte Gaffar*, the claim at issue is a composition claim for oral treatment, and it reads:

> 1. An oral care composition comprising about 0.1 % to about 5% of a tocopherol component, wherein the tocopherol component consists of about 50% to about 90% by weight of gamma tocopherol and the balance of the tocopherol component is selected from alpha tocopherol, beta tocopherol, delta tocopherol, and mixtures thereof.[198]

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[193] *Id.*at 9.
[194] *Id.*at 10.
[195] *Id.*
[196] *Id.* at 10-11.
[197] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) (Citing *Shell Development Co. v. Watson*, 149 F.Supp. 279, 280 (D.C.1957)).
[198] *Ex Parte Gaffar*, Appeal 2013-001533, 2015 WL 7720188, at 1 (Oct. 26, 2015).

The Examiner rejected the claim as obvious over prior art Hansenne.[199] Hansenne taught tocopherol/melanin[-]like pigment combination was useful for oral and dental use, and the combination included a "mixture of a-tocopherol, β -tocopherol, γ-tocopherol and δ-tocopherol in a ratio of 25/25/25/25, dissolved in soya oil at a concentration of 50%."[200] Patent applicants appealed the decision to the PTAB and contended that the lead compound (or lead formulation) analysis was required.[201] Under the analysis, the applications alleged, the prior art had to include specific subject matter, not hypothetical and unexemplified examples or combinations selected with hindsight.[202] The applicants contended Hansenne did not teach or suggest a tocopherol component with 50% to 90% of gamma tocopherol by weight.[203]

The PTAB affirmed Examiner's rejection and found LCA was not required for a composition or formulation claim.[204] Although the Federal Circuit had stated in *Unigene Labs., Inc. v. Apotex, Inc.* that the obviousness analysis in the chemical art was often based on a lead compound and "that in the context of a composition or formulation patent the 'lead compound' might more appropriately be referred to as a 'reference composition,'" the PTAB found the two-prong LCA analysis was not required in every composition or formulation claim analysis.[205]

Similarly, the PTAB declined to follow the LCA in another case of composition claims directed to a dietary supplement.[206] The PTAB agreed with the Examiner that the rationale for obviousness analysis of a chemical compound is "entirely different than that of compositions."[207]

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[199] *Id.*
[200] *Id.* at 2.
[201] *Id.* at 3.
[202] *Id.*
[203] *Id.*
[204] *Id.* at 1, 3.
[205] *Id.* at 3 (Citing *Unigene Labs., Inc. v. Apotex, Inc.* 655 F.3d 1352, 1361-62 (Fed. Cir. 2011)).
[206] *Ex Parte Rabovsky*, Appeal 2015-006014, 2016 WL 6560227, at 1 (Nov. 1, 2016).
[207] *Id.* at 4.

"A single chemical change on a compound can render a drug much improved or useless for its purpose. The addition or subtraction of a component does not alter the ability of the composition to serve as a dietary supplement." The obviousness of components of a composition or claimed range of the components can be based on rationale, case law and guidance, not a single specific composition in the prior art.[208]

ii. LCA Is Required for Obviousness of New Chemical Compound

Although the USPTO does not require the LCA in every chemical genus or composition case, it requires the LCA in the obviousness analysis of new chemical compounds.

In *Apotex Inc. v. Merck Sharp & Dohme Corp.*, Apotext filed a Petition for an IPR to challenge Merck's patent covering fosaprepitant dimeglumine, which is useful for treating inflammatory diseases, pain or migraine, asthma, and emesis, and is the active ingredient in Merck's FDA-approved drug Emend® for Injection.[209] Apotex claimed that fosaprepitant dimeglumine was obvious over prior art compounds, especially a specific example, compound 96 disclosed in a prior patent.[210]

The PTAB made it clear that the LCA is generally required in a case of new chemical compound, and stated "[e]ven 'post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.'"[211] In determining whether a PHOSITA would have selected the Compound 96 as the lead compound, the PTAB followed the reasoning of the Federal Circuit in *Otsuka* and *Altana*, as determined by the pertinent properties of the prior compound.[212] The PTAB noted Compound 96 was among

[208] *Id.*
[209] IPR2015-00419, 2015 WL 4036000, at 1-2 (June 25, 2015).
[210] *Id.* at 4.
[211] *Id.* (Citing *Eisai*, 533 F.3d at 1359).
[212] *Id.* at 5.

the "laundry list" of 601 compounds disclosed in the prior art and there was no reported activity data for those compounds, so there was no reason for a PHOSITA to select any of the compounds as a lead, and compound 96 could not be "a natural choice for further development."[213] Therefore, the PTAB denied the institution of *inter partes* review by concluding that Apotex had not established a reasonable likelihood that it would prevail in showing the unpantentavility of the claim.[214]

Similarly, in *Ex Parte Caligiuri*, the PTAB emphasized the importance of the pertinent properties in selecting the lead compound even though the identified lead compound was among twenty compounds listed in the prior art.[215] In this case, the Examiner identified compound 0477 in the prior art as structurally related to the claimed compound and was specifically identified in the prior art among other 19 listed compounds.[216] In reversing the Examiner's Final Rejection on obviousness of the claimed compounds, the PTAB reasoned that absence any functional data of compound 0477, or suggestion that 0477 provided any benefit or special property as compared to others disclosed compounds in the prior art, the identification of 0477, even among a small number of compounds, was not sufficient for a PHOSITA to select compound 0477 as the lead compound.[217]

Once pertinent properties are disclosed in the prior art, the PTAB is likely to find that there is sufficient motivation for a PHOSITA to select any of the structurally similar compounds identified in the prior art.

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[213] *Id.* (Citing *Altana Pharma AG*, 566 F.3d at 1008).
[214] *Id.* at 7.
[215] *Ex Parte Caligiuri*, Appeal 2012-007499, 2015 WL 1262961, at 4 (Mar. 17, 2015).
[216] *Id.* at 3-4.
[217] *Id.* at 4.

In *Ex Parte Demattei*, patent owners appealed the Examiner's rejection of a patent claiming hydrogen sulfate salts.[218] The Examiner found the claimed salts were obvious over a prior art patent's disclosure of a structurally similar compound 29c.[219] The prior art also disclosed the MEK1 inhibition activity of a list of compounds, and twelve compounds, including compound 29c, were identified as active with an IC50 value of less than 50μm.[220] The PTAB found any of the disclosed twelve compounds could be selected by a PHOSITA to serve as lead compounds.[221]

Similarly, in *Ex Parte Baranowska-Kortylewicz*, the PTAB found any of the six compounds highlighted in the prior art reference could have been looked at by a PHOSITA as lead compounds even though the properties of some compounds might be "detrimental" to their therapeutic effect.[222] In this appeal of Examiner's rejection, the invention relates to compounds that produce cytotoxic effect and/or detectable via medicine imaging techniques by being incorporated into nucleus of malignant tumor cells.[223] A prior art reference disclosed a general formula of conjugate and six specific examples having similar formulas as the invented compounds.[224] The prior art described the conjugates were capable of targeting tumor cells and being incorporated into the nuclear material to produce a cytotoxic effect.[225] The testing data showed that the example 1 was very effective, but had a short half-life, which might be

[218] *Ex Parte Demattei*, Appeal 2012-003219, 2013 WL 3817453, at 1 (July 22, 2013)
[219] *Id.*
[220] *Id.*
[221] *Id.* at 2.
[222] *Ex Parte Baranowska-Kortylewicz*, Appeal 2015-006217, 2016 WL 7474877, at 5 (Dec. 13, 2016).
[223] *Id.* at 1.
[224] *Id.* at 2.
[225] *Id.*

"detrimental to the delivery of therapeutic dose to tumor."[226] However, the prior art also stated the short half-life could be beneficial due the possibility of repeated injection without a large radioactive burden in normal tissue.[227] The prior art also disclosed that example 2 could not cross cell membrane by itself and required transport mechanism because of its hydrophilicity, while example 5 was the most hydrophobic and might be best suited for local administration.[228] Citing *Otsuka*, the patent owner contended a PHOSITA would not have selected example 1 or 2 as lead compounds because of their nonbeneficial properties, and the prior art taught away from selecting them.[229] Instead, example 5 is the natural choice for further development.[230] The PTAB disagreed and found the prior art taught the compounds were useful for their "cytotoxic effect *and/or* . . . radioimaging techniques."[231] Although example 1 had short half-life and example 2 was hydrophilic, the prior art clearly taught the means to overcome the problems, so a PHOSITA would not have been dissuaded to select them as lead compounds.[232] Also citing *Otsuka*, where the Federal Circuit "expressly acknowledges the possibility that there can be 'one or more lead compounds," the PTAB found any one of the six examples could be selected as the lead compound by a PHOSITA.[233]

3. The Differences Between the Court Decisions and USPTO Decisions

Because the USPTO follows the Federal Circuit decisions, the PTO has applied and followed the LCA in its obviousness analysis in the chemical art. For example, both Federal Circuit and the USPTO emphasized the importance of the pertinent property data in the prior art

[226] *Id.*
[227] *Id.*
[228] *Id.* at 3.
[229] *Id.* at 4.
[230] *Id.*
[231] *Id.* at 5.
[232] *Id.*
[233] *Id.* at 4-5.

for a PHOSITA to select the prior art compound as the lead compound. However, there are a few noticeable differences.

First, the USPTO explicitly stated LCA is not required for the obviousness analysis of every genus and composition claims.[234] This is in contrast with the Federal Circuit's approach in *Unigene Labs, Inc. v. Apotex, Inc*. In *Unigene*, Unigene Laboratories, Inc. and Upsher–Smith Laboratories, Inc. (Unigene) owned a patent claiming an FDA approved nasal spray Fortical® with the active ingredient salmon calcitonin, a natural polypeptide hormone.[235] Apotex filed an ANDA and contended the composition claim in Unigene's patent was obvious over prior art, including Novartis International AG's Miacalcin® calcitonin nasal spray.[236] Fortical® and Miacalcin® have the same active ingredient and are bioequivalent, but they have different formulations.[237] Miacalcin® contains benzalkonium chloride (BZK) as a preservative, absorption enhancer and surfactant.[238] Fortical® contains 20mM citric acid as an absorption enhancer and stabilizer/buffer, polyoxyethylene(2) sorbitan monooleate as a surfactant, and phenylethyl alcohol and benzyl alcohol as preservatives.[239] The court followed the LCA and found Miacalcin® served as the reference composition for the development of the claimed composition because they had the same function and pharmaceutical properties.[240] However, the court found there was no reason or motivation for a PHOSITA to replace BZK in Miacalcin® with 20 mM of citric acid in the normal course of research and development of nasal calcitonin formulation, and

[234] *Ex Parte Argade*, 2016 WL at 9; *Ex Parte Rabovsky*, 2016 WL, at 1.
[235] *Unigene*, 655 F.3d at 1355.
[236] *Id.*at 1356, 1362.
[237] *Id.*at 1355-56.
[238] *Id.* at 1356.
[239] *Id.*
[240] *Id.* at 1361-62.

would not make a combination of citric acid with polyoxyethylene(2) sorbitan monooleate, phenylethyl alcohol and benzyl alcohol.[241]

Although the Federal Circuit has not ruled the LCA is required for the obviousness analysis of each chemical composition or formulation patent, it followed the LCA in *Unigene* and referred the lead compound equivalent of chemical composition as "reference composition."[242] However, in multiple USPTO cases, the PTAB has found the LCA was inapplicable in the obviousness analysis of those genus and composition claims, and reasoned that structural changes of chemical compound could have much more impact on the function and properties of a drug than impact of formulation changes on the drug.[243] The PTAB noted "[i]ndeed, *Unigene* cannot run counter to the flexible analysis set out by the Supreme Court in *KSR* that recognizes the obviousness of pursuing known options within the technical grasp of the skilled artisan."[244]

The second difference is that once prior art has sufficient disclosure of prior art compounds' pertinent properties, in USPTO's view, all those compounds could serve as lead compounds, and the USPTO does not examine further in detail whether a PHOSITA would pick one or a few of the limited number of disclosed compounds. In *Ex Parte Dematteі*, the PTAB found any of the twelve compounds disclosed in the prior art with MEK1 inhibition activity could be selected by a PHOSITA as lead compounds.[245] Similarly, in *Ex Parte Baranowska-Kortylewicz*, the PTAB found any of the six compounds highlighted in the prior art reference

[241] *Id.* at 1363-64.
[242] *Id.* at 1362.
[243] *Ex Parte Rabovsky*, 2016 WL, at 4.
[244] *Id.* at 5.
[245] *Ex Parte Dematteі*, 2013 WL at 2.

could have been looked at by a PHOSITA as lead compounds even if some of them presented negative properties such as short half-life or difficulty in crossing membrane.[246]

However, in *Otsuka*, the Federal Circuit found in the eleven compounds identified in the prior art with mouse jumping test data, the fifth potent compound would not have been considered by a PHOSITA as a lead compound because of the other four more attractive lead compound candidates. Also, the court tends to find that any negative properties of the prior art compound could dissuade the PHOSITA to select the prior art compound as the lead. Compound b's effect in increasing body weight and brown fat weight in *Taketa* led the court to conclude there was no motivation to select compound b.[247] This is in contrast with the result in *Ex Parte Baranowska-Kortylewicz*, where the PTAB found the short-half life and hydrophilicity of the prior art compounds did not teach away the selection of the compounds as lead compounds.[248] Although the Federal Circuit has recognized the possibility of "one or more lead compounds," courts appear to have narrower focus on the lead compound.[249]

The more relaxed application of the LCA at the USPTO may be due to the different evidentiary burden of the proceedings. In court litigations, a patent is presumed to be valid.[250] The accused infringer has the burden to show every element of the obviousness of the patent by clear and convincing evidence.[251] Thus, in the LCA, the infringer has to prove by clear and convincing evidence that a PHOSITA would have selected the presented prior art compound as the lead compound, and by clear and convincing evidence that the PHOSITA would have modified the lead compound in a specific way to achieve the patented compound. In PTO

[246] *Ex Parte Baranowska-Kortylewicz*, 2016 WL at 5.
[247] *Takeda*, 492 F.3d at 1358-60.
[248] *Ex Parte Baranowska-Kortylewicz*, 2016 WL at 5.
[249] *Otsuka*, 678 F.3d at 1291.
[250] 35 U.S.C. § 282
[251] *Takeda*, 492 F.3d at 1355.

proceedings, there is no presumption of validity of the challenged patents. The standard of proof for *ex parte* appeal is preponderance of evidence, and reasonable likelihood of prevailing for IPR proceedings. The patent challenger only needs to prove it is reasonably likely the PHOSITA would have selected the compound and modified the compound to make the new chemical compound. The standard is lower than the clear and convincing evidence in court proceedings, which explains why the PTAB tends to find all limited number of compounds with favorable properties are possible lead compounds.

V. THE LCA IS PROPER AND CONSISTENT WITH THE *KSR* RATIONALE

Since the Federal Circuit adopted the LCA and continued to use it in post-*KSR* decisions, the LCA has been criticized by many as rigid and bright line rule that is inconsistent with the *KSR* flexible requirement.[252] However, the LCA is required by the technology and modern drug discovery process, and a analysis of the court decisions shows the LCA is not inconsistent with *KSR*.

A. The LCA Is Determined by the Modern Drug Discovery Process

The LCA was developed with the modern drug discovery development, and it is consistent with the process of target identification and validation, high throughput screening, hit-to-lead and optimization steps. As illustrated before, the modern discovery is no longer based on accidental discovery or scientists' imagination, but a target oriented rational drug discovery. Under the traditional approach, a scientist may pick an interested molecule without knowing the mechanism of the action, and makes some random modifications to the structure, in the hope this would lead to compounds with similar or more potent activities. If the scientist is fortunate enough, his efforts may eventually lead to the development of a drug.

[252] *Supra* note 8.

Under the modern approach, the target protein was studied and the mechanism of its interaction with certain classes of chemical compounds was understood first. Based on the knowledge of the target protein and prior art disclosure of the chemical classes likely to have activity at the target site, library compounds are prepared and screened to yield hits series. After further analysis and screening, the hits were narrow further to give more potent and selective compounds, with less toxicity and other side effects, but with desirable absorption, distribution, metabolism and excretion. Therefore, the selection of compounds for further development is a rational, property-based process rather than a random, serendipitous process under the traditional approach.

This higher intellectual input in the modern drug discovery is consistent with the higher requirement of finding of obviousness under the LCA than the "structural similarity" approach. Under the LCA, a reason or motivation is required for a PHOSITA to select the prior art compound as the lead compound for further development. In the property driven drug discovery process, a PHOSITA faces with a large number of chemical compounds, either prepared by himself, or from literature and patent precedents, sometimes thousands of compounds with potential favorable activities. The PHOSITA needs to make choices based on knowledge of the target and compounds' properties, not just potency and selectivity, but also toxicity and other unfavorable side effects, as well as ADME properties. If there is no property data or other motivations, it is impossible for a PHOSITA to go further in the process. He or she would not randomly choose compounds for further development, and hope they make to the final drug.

The LCA also requires a motivation to modify the prior art compound to arrive at the claimed compound. This is determined by the drug discovery process as well as the characteristics of chemical art. During drug discovery, modification of chemical structures

happens at every stage from hit identification, hit-to-lead and lead optimization. A PHOSITA has to modify compounds based on the properties from the assays, from the interaction of the compounds with the target, and from the knowledge and experience of chemical synthesis. Because the infinite possibility of variations of a chemical structure, a PHOSITA needs to know which part of a chemical structure should be modified and at which position; which substituents are suitable to obtain favorable properties; which chemical modification is easy to synthesize and suited for large scale productions. Each decision requires input from different expertise, and thus the resulting chemical compounds are not the result of a simple, random modification, but an intense intellectual process.

B. LAC Is Consistent with KSR

Although the LCA requires reason or motivation to select and modify lead compounds, it is not in conflict with the *KSR* decision, and courts have considered various factors consistent with the *KSR* rational in applying the LCA.

1. Motivation Requirement Is Consistent with *KSR*

Although the TSM was rejected as the exclusive approach for obviousness analysis by the Supreme Court, "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."[253] As the Federal Circuit noted, the Supreme Court in *KSR* for the obviousness analysis assumed a PHOSITA would recognize a problem and pursues potential solutions, and there would be a reason or motivation for the PHOSITA to make particular modifications and to narrow the prior art scope to a limited

[253] *Takeda*, 492 F.3d at 1356–57 (Quoting *KSR*, 127 S.Ct. at 1731).

number of predictable solutions.[254] Whether the reason is the demand from the marketplace, any need or problem in the field, knowledge or common sense of the PHOSITA, there exists such a reason or motivation to choose the prior art elements and combine or modify such elements to arrive at the claimed invention. A PHOSITA would not just pick some elements from prior art without any reason and then combine or modify them. Even for the "obvious to try" rationale, the motivation comes from the "identified, predictable" solution within the PHOSITA's reach.[255]

In the case of chemical art, it is especially important for a PHOSITA in the drug discovery process to have some reason or motivation to select and modify the prior art compounds. This is determined by the problem or difficulty in the drug discovery, the complicity of the process, and the intellectual requirement in each step of the process. Also, because of the nature of chemical art, a slight variation of a chemical structure can lead to completely different properties. The solutions to a chemical problem are likely unpredictable, and anticipated results are less likely in the chemical art. This is especially true in the drug discovery field since any negative property or side effect could lead to the failure of the program. Therefore "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound,"[256] and "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."[257]

[254] *Eisai*, 533 F.3d at 1359.
[255] *KSR*, 550 U.S. at 402.
[256] *Eisai*, 533 F.3d at 1359.
[257] *Takeda*, 492 F.3d at 1357.

2. *KSR* Rationales Are Considered in LCA

In consistent with the *KSR*, the Federal Circuit has stated the motivation does not have to explicitly come from the prior art, and it can come from any number of sources.[258]

i. The Number of Compounds Disclosed

In determining whether a PHOSITA would have select the prior art compound as the lead compound, both Federal Circuit and the PTO have considered the disclosure of the prior art as a whole. The number of potential lead compounds disclosed in the prior art is an important factor in the consideration. In *Altana*, the Federal Circuit noted compound 12 was disclosed in the prior art among seventeen other compounds with improved activity over omeprazole, and compound 12 was one of the more potent of the eighteen compounds in the prior art with the activity data.[259] The court concluded the defendant had raised a substantial question that a PHOSITA would have selected the more potent compounds among the eighteen compounds, including compound 12 as the lead compound.[260]

However, when there are a large number of options in the prior art, the court is less likely to find a compound to be a lead compound. In *Otsuka*, where the prior art included a laundry list of compound with potential central nervous system controlling properties, and the presented lead compound was buried in hundreds of examples, the presented compound was not considered a lead compound. [261]

Therefore, by considering the number of the potential lead compounds disclosed in the prior art, courts and the PTO followed the *KSR*'s rationale that when there are "finite number of"

[258] *Eisai*, 533 F.3d at 1357.
[259] *Altana*, 1007-08.
[260] *Id.* at 1009.
[261] *Otsuka*, at 1294-95.

solutions, a PHOSITA would likely pursue one or more of the solutions.[262] This is not a motivation explicitly from the prior art, but from the knowledge or common sense of the PHOSITA, which is consistent with the *KSR*'s flexible requirement.

ii. State of the Art and the Knowledge of the PHOSITA

In determining the obviousness of the chemical compound, the Federal Circuit considered the state of the art at the time of the invention, not just the teaching of the specific prior art, for a PHOSITA to select and modify the prior art compounds.

In *BMS*, the structure of entecavir contains a "carbocylic ring."[263] The court examined the scientific literatures during the relevant time period before the claimed invention, and found that carbocyclic analogs were of great interest to scientists in search of compounds with antiviral activity at that time.[264] There were extensive research and publications on carbocyclic analogs and 2'-CDG (one of the analogs) for their antiviral activities.[265] 2'-CDG was a hot molecule because of its potency and non-toxicity, and it was treated by different researchers as exciting and promising compound to work with.[266] The expert testimony also showed 2'-CDG's prominence during the relevant time frame.[267] These evidence on the state of the antiviral drug research on carbocyclic analogs gave the court sufficient ground to find a PHOSITA would have selected the carbocyclic analog 2'-CDG as the lead compound.[268] Here, among the various antiviral drug discovery approaches, the research on the carbocyclic analogs as a promising area

[262] *KSR*, 550 U.S. at 421.
[263] *BMS* 752 F.3d at 970.
[264] *Id.* at 974.
[265] *Id.* at 971-74.
[266] *Id.* at 971.
[267] *Id.* at 975.
[268] *Id.*

during the time of the invention narrowed the focus in the search of the lead compound, and provided the motivation to select 2'-CDG.

In *BMS*, the court also found the motivation to modify 2'-CDG from the knowledge of the PHOSITA.[269] From expert testimonies, the court noted small, conservative changes to the 2'-CDG structure were well within a PHOSITA's reach. Based on the PHOSITA's knowledge, he or she could identify the specific part of the structure to make changes for better activity and easy synthesis.[270] The PHOSITA would then combine his knowledge and the prior art disclosure to make the changes at the specific site, and the options were finite and easily traversed.[271]

These considerations by the court follow *KSR*'s flexible requirement that any problem or need in the field, interrelated teachings of prior art reference, or background knowledge of a PHOSITA could provide the reason or motivation to combine or modify the prior art elements.

iii. Obvious to Try

In *KSR*, the Supreme Court noted if "there are a finite number of identified, predictable solutions," it is obvious for a PHOSITA to try the combination, and "[i]f this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.[272] Because chemical art is generally an unpredictable art, it is difficult for a PHOAITA to identify a finite number of predictable solutions. *KSR*'s obvious to try "may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."[273] However, the Federal Circuit has incorporated this obvious to try rationale in the application of the LCA under certain circumstances.

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[269] *Id.*
[270] *Id.*
[271] *Id.* at 976.
[272] *KSR*, 550 U.S. at 421.
[273] *Eisai*, 533 F.3d at 1359.

In examining the motivation to select lead compounds, courts and the USPTO have recognized the limited number of potential lead compounds disclosed in the prior art presents a situation of finite number of solutions, so a PHOSITA would likely pursue one or more of the solutions.[274]

Takeda and *BMS* illustrate the applicability of the obvious to try rationale in the analysis of the motivation for chemical modifications. In *Takeda*, the Federal Circuit found the process of replacing the methyl group with an ethyl group on the pyridyl ring of the prior art compound and moving the ethyl from the 6-position to the 5-position was not routine at the time of the invention.[275] A PHOSITA would have to look at various substituents, such as chlorides, halides, and other groups, not just methyl in modifying the pyridyl ring.[276] There were infinite number of substituents to consider, and there were no expectation of success in reducing or eliminating toxicity of compound b by any particular substituent, so a PHOSITA would not be motivated to modify in this particular way.[277] Because there were no finite number of solutions and no anticipated success for the modification, the modification would not have been obvious to a PHOSITA.

In contrast, the addition of a single carbon atom to form an exocyclic methylene with the carbon atom at the carbocyclic ring of 2'-CDG in *BMS* was a modification within a small, finite number of changes to try to arrive at the claimed compound entecavir.[278] The expert testimony in *BMS* showed that in considering whether to modify 2'-CDG's carbocyclic ring or its guanine base, experts agreed carbocyclic ring would be a natural decision because of possible greater

[274] *Supra* note 259.
[275] *Takeda*, 492 F.3d at 1360.
[276] *Id.*
[277] *Id.* at 1360-61.
[278] *BMS* 752 F.3d at 975-76.

activity from this modification.[279] After this decision, the court found a PHOSITA would then make changes on either the 2' or 5' position on the carbocyclic ring because these are the only positions where small modifications are possible.[280] As to what small changes to make, the court found the disclosure of the prior art, the properties of other antiviral compounds, and the strategy in synthesis narrowed the choice of changes to a finite number of solutions.[281] Because structurally similar compounds often have similar properties, there was reasonable expectation of success at the time of the invention.[282] In this analysis, the court considered the knowledge of the PHOSITA and the disclosure of the prior art to narrow the potentially infinite solutions to a finite number. Because of the reasonable expectation of success, the solutions were obvious to try.

VI. CONCLUSION

As drug discovery evolves from a serendipitous discovery to rational design and discovery, the obviousness analysis of chemical compounds evolves from structural similarity determinative to property determinative. The Lead Compound Analysis was in response to the development of modern drug discovery. It requires a patent challenger to prove a PHOSITA would have been motivated to select the prior art compound as the lead compound for further development, and would have been motivated to modify the compound to make the claimed invention. Although courts and the USPTO require different burden of proof to establish a *prima facie* obviousness, they have generally applied the LCA consistently to require the property data or other motivations to select the prior art compound as the lead and to modify the compound.

The LCA has been criticized as rigid and inconsistent with the *KSR* decision. However, the LCA is determined by the nature of chemistry, and the development of technology and drug

[279] *Id.* at 975.
[280] *Id.*
[281] *Id.* at 975-76.
[282] *Id.* at 976.

discovery. A reason or motivation is required in every step of the drug discovery, from design of the chemical compound, hit identification, hit to lead and lead optimization. Analysis of the *KSR* and the LCA cases reveals that the motivation requirement is not in conflict with the *KSR* decision. Consideration of various factors by courts and the USPTO in the analysis, including the number of compounds disclosed in the prior art, the interrelated teaching of the prior art references, the state of the art at the time of the invention, knowledge of the PHOSITA, and the obvious to try approach, demonstrates the LCA is proper and in line with the *KSR* decision.