Marquette Intellectual Property Law Review

Volume 16 | Issue 2 Article 1

Summer 2012

Structural Uncertainty: Understanding the Federal Circuit's Lead Compound Analysis

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ARTICLES

STRUCTURAL UNCERTAINTY: UNDERSTANDING THE FEDERAL CIRCUIT'S LEAD COMPOUND ANALYSIS

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I. INTRODUCTION

Recently, the Federal Circuit and lower courts have applied a new test to assess the question of obviousness for chemical compounds. While courts have always considered the presence of some lead compound to be relevant to the question of obviousness, beginning at the turn of the millennium, the Federal Circuit began assessing obviousness in a more formulaic fashion, applying what is commonly referred to as the lead compound analysis to determine if a litigant has

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established a prima facie case of obviousness.

This Paper describes the development of the lead compound analysis,[1] and its application.[2] This Paper then discusses some of the shortcomings and weaknesses of the doctrine's applications[3] and how understanding the lead compound analysis and how it is likely to be applied in typical situations can be useful in understanding both how to draft stronger patents and what ways might be available to attack the obviousness of a chemical compound or a court's application of the lead compound analysis.[4]

A. Obviousness and Chemical Compounds

While the obviousness analysis has always been factually intensive, the parameters for assessing obviousness have remained relatively steady since the United States Supreme Court first addressed obviousness under the 1952 Patent Act in *Graham v. John Deere Company*.[5] In *Graham v. John Deere* the Supreme Court laid out four factors for approaching obviousness. First, the scope and the content of the prior art and the claims should be determined.[6] Second, the differences between the prior art and the claims at issue must be ascertained. Third, the level of ordinary skill in the art is determined. And finally, courts consider additional factors such as the commercial success, long felt but unresolved needs, and failure of others.[7]

The Supreme Court's most recent take on obviousness emphasized that the *John Deere* factors still defined the controlling inquiry.[8] In *KSR v. Teleflex*, the Supreme Court held that the Federal Circuit's teaching suggestion motivation (TSM) test was overly rigid and the Court emphasized that any approach to obviousness must be a flexible approach.[9] Under the TSM test, the Federal Circuit would determine obviousness of a combination by looking to see if the prior art had some teaching, suggestion, or created some motivation to combine certain elements in the way that the invention did.[10] If a court found that the

1. *See infra* Part IA–IB.
2. *See infra* Part IC.
3. *See infra* Part II.
4. *See infra* Part III.
5. Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966).
6. *Id.* at 17–18.
7. *Id.*
8. KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398 (2007).
9. *Id.* at 419.
10. *Id.* at 418.

prior art did contain a teaching, suggestion or motivation, the invention would be obvious.

The TSM test was a high standard for proving obviousness of a chemical compound because it required the prior art to contain language not often found, suggestions of what could be done. *KSR* lowered the standard for asserting obviousness, holding that the Federal Circuit's standard was not the only approach to obviousness, and that using it alone constituted too rigid of an analysis. After *KSR*, while a teaching suggestion or motivation might be relevant, lower courts are free to look at things outside the prior art, such as common sense and ordinary creativity.[11]

In the earliest cases at the Court of Customs and Patent Appeals (C.C.P.A.) specific to chemical compounds, structural similarity was deemed as sufficient to support a finding of obviousness.[12] A person who knew the structure of a related compound would then, in turn, be motivated to make analogs of that compound. However, as technology for elucidating structures came on the market, and more structures became known, courts, perhaps recognizing the complexity and unpredictability of chemical compounds,[13] moved away from the assumption that once a structure was known, it would be obvious to test all the analogs for similar properties.

In the 1970s, the C.C.P.A. found that prior art disclosure of a structural analog alone was insufficient to provide real motivation to make a new compound.[14] In *Stemniski*, the applicant claimed a tin composition useful in lubricants as an antioxidant while the prior art analog compositions had no known utility.[15] The court decided that without a known utility for the prior art compound, the applicant had no

11. *Id.* at 420 ("Common sense teaches, however, that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.").

12. *See*, *e.g. In re* Riden, 318 F.2d 761 (C.C.P.A 1963); *In re* Henze, 181 F.2d 196 (C.C.P.A. 1950).

13. Indeed, there are several examples of chemical compositions that are structurally similar, but have widely diverging properties. A common example is thalidomide, a drug developed in the 1950s. The drug contained two enantiomers, which are compounds that differ only in their configuration at one site, that is, the atoms have the exact same configuration. One enantiomer of thalidomide helped people suffering from insomnia to sleep, however, the other enantiomer caused deformities in unborn children of the patients who took the drug. *See* GARETH THOMAS, MEDICINAL CHEMISTRY: AN INTRODUCTION, 38 (2d ed. 2007).

14. *In re* Stemniski, 444 F.2d 581, 581 (C.C.P.A. 1971).

15. *Id.* at 582.

reason or motivation to synthesize the claimed analogs.[16] It was also immaterial that the prior art compounds actually had these properties since they were unknown at the time of invention.[17]

A subsequent line of cases confirmed *Stemniski*.[18] These cases mainly conclude that some utility is required for the prior art compound to give a person of ordinary skill in the art the requisite motivation to synthesize analogs.[19] This new approach not only allowed for the patenting of a large number of chemical compounds, but also confirmed the idea that structural similarity for chemical compounds is more unpredictable than the structural similarity of other systems. For example, two mechanical structures with a substantially similar structure are likely to operate in the same way, but chemical compounds do not operate under this same assumption. In contrast, chemical compounds display a wide range of properties from their steric effects to the electronic effects of substitutions, as well their interactions with chiral systems such as the body.

With the switch from the C.C.P.A. to the Federal Circuit, the Federal Circuit considered what is still considered a lead case for the obviousness of structurally similar chemical compounds en banc in *In re Dillon*.[20] In *Dillon*, a patent applicant claimed a composition of hydrocarbon fuel and tetra-orthoester, producing less soot during combustion, but the prior art disclosed the use of tri-orthoesters in fuel for dewatering purposes and of tetra-orthoesters as water scavengers in hydraulic fluids. Tri-ortho esters differ from tetra-ortho esters in the addition of one ester group to the compound. The Board of Patent Appeals and Interferences found that the claims were *prima facie* obvious in light of the prior art.[21] The court found that the "sufficiently close relationship" between the tri-orthoesters and the tetra-ortho-esters and the knowledge within the prior art created an expectation that the tetra-esters would have the same or similar properties as the tri-esters.[22]

The Federal Circuit summarized the analysis as having different considerations: (1) "the new compound or composition [must be] []

16. *Id.* at 587.

17. *Id.*

18. *See, e.g., In re* Gyurik, 596 F.2d 1012, 1018 (C.C.P.A. 1979) (noting that a structural analog was not obvious based on a reaction intermediate).

19. *Id.*

20. *In re* Dillon, 919 F.2d 688 (Fed. Cir. 1990).

21. *Id.* at 692.

22. *Id.*

structurally similar to the reference compound or composition," and (2) that "there is some suggestion or expectation in the *prior art that the new compound or composition* [would] [] have the *same or similar utility* as [the compound asserted by the applicant] []."[23] If the previously disclosed properties of a prior art compound provided sufficient motivation to trigger a *prima facie* obviousness rejection, even though the new compound has unrelated, different, and unexpected properties, the analysis then turns to rebuttal, by showing that his compound has unexpected properties relative to prior art compounds, "that the prior art was so deficient that there was no motivation to make what otherwise might appear to be obvious changes," or any other pertinent argument.[24]

B. Development of Lead Compound Analysis

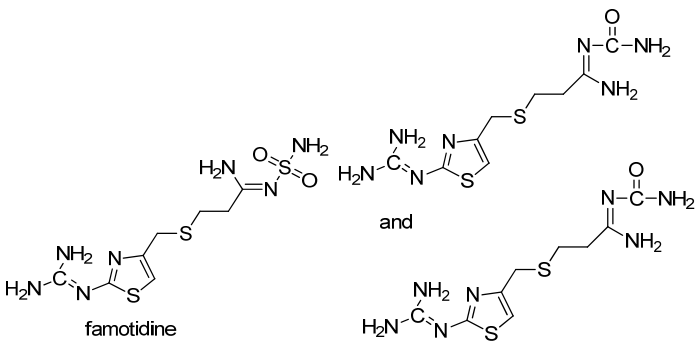
The earliest case establishing the modern "lead compound" analysis is *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc*.[25] *Yamanouchi* was the result of a successful motion for judgment as a matter of law (JMOL) upholding the validity of the '408 patent.[26] The '408 patent was directed at compounds that inhibit gastric acid secretion.[27] At issue was a claim for the compound famotidine.[28] Famotidine is a member of a larger class of compounds called histamine$_2$ (H_2) antagonists, which have a general structure containing a substituted heterocycle which is connected to a polar tail by an "alkyl containing" chain.[29] Danbury filed an Abbreviated New Drug Application (ANDA) with the Food and Drug Administration (FDA) and made a Paragraph IV certification that the patent on famotidine was invalid.[30] Paragraph IV certifications are considered acts of infringement,[31] and after receiving the certification, Yamanouchi filed suit.

At the district court, Danbury argued that famotidine was invalid as an obvious result of combining features of compounds from the prior art, and then performing a bioisosteric substitution to reach resulting

23. *Id.*
24. *Id.* at 692–93.
25. Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339 (Fed. Cir. 2000).
26. *Id.* at 1341.
27. *Id.*
28. *Id.*
29. *Id*.
30. *Id.* at 1342.
31. 35 U.S.C. § 271 (e)(2) (2010).

compound.[32] Specifically, Danbury presented two H_2 antagonists from the prior art, tiotidine and E44, and argued that famtotidine was the result of combining the heterocylce of tiotidine with the polar tail of E44 followed by a routine bioisosteric substitution of a sulfomoyl group for a carbamoyl group substitution in the polar tail.[33]

The Federal Circuit upheld the JMOL noting at the outset that Danbury did not show the motivation for selecting either of the compounds.[34] While the E44 showed increased activity, the court noted that the activity alone was not a sufficient motivation to choose E44 as a lead compound because other compounds had been shown to be more active.[35] The court further noted that Danbury had failed to show the motivation to combine the heterocycle of tiotidine with the polar tail of E44.[36] An expectation that the compound would show baseline H2 antagonist activity was not enough to show the reasonable expectation of success for the compound.[37] Finally, the court noted that the prior art did not suggest any order of manipulating the compounds, so there was no teaching that would have led a person having ordinary skill in the art to follow the steps of combining the two parts of different molecules, then making the bioisosteric substitution.

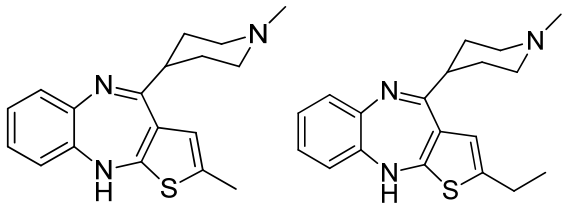


The analysis in *Yamanouchui* was applied again in *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*; however, in *Lilly* the analysis of *Yamanouchi* was transformed into a requirement. In *Lilly*, IVAX Pharmaceuticals, Inc. (formerly Goldline) filed an ANDA Paragraph IV

32. *Yamanouchi*, 231 F.3d at 1343–44.
33. *Id.*
34. *Id.* at 1345.
35. *Id.*
36. *Id.*
37. *Id.*

certification to make Lilly's Zyprexa. IVAX asserted that Lilly's patent on the active ingredient in Zypreza, olanzapine, was invalid as obvious.[38]

IVAX argued that olanzapine was obvious based on a prior art reference to ethyl olanzapine. Ethyl olanzapine has a similar structure to olanzapine differing only in that ethyl olanzapine has an ethyl rather than a methyl group on the thiophene ring.



IVAX argued that the structural similarity made them *prima facie* obvious, but the district court rejected IVAX's arguments. Instead, the district court applied the two step analysis from *Yamanouchi* to determine whether there was a *prima facie* case of obviousness.[39] On appeal, IVAX argued that the district court had erred by requiring as a "threshold requirement" a teaching or incentive to treat the closest prior art as a lead compound.[40] The Federal Circuit affirmed the decision below and likened the case to *Yamanouchi*; however, unlike the district court, the Federal Circuit did not cite *Yamanouchi* as the source of its two step analysis. Despite not citing *Yamanouchi* in the same way as the district court, the Federal Circuit undertook the same analysis as the district court finding first that IVAX had failed to prove that ethyl olanzapine was the lead compound. Despite its structural similarity, the prior art had taught that an electron withdrawing group on the benzene ring improved activity.[41] Next, the court further noted that even if ethyl olanzapine would have been a lead compound, the law *required* motivation to modify the prior art compound into the claimed invention.[42]

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38. *See* Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369, 1380 (Fed. Cir. 2006).

39. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc, 364 F. Supp. 2d 820, 904 (S.D. Ind. 2005).

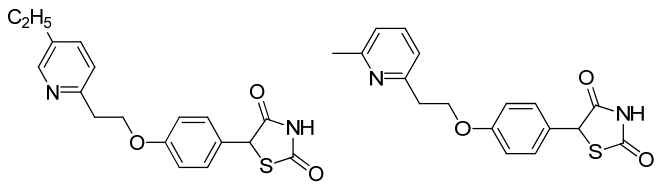
40. Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369, 1377 (Fed. Cir. 2006).

41. *Id.* at 1374.

42. *Id.* at 1379.

The Federal Circuit gave more clarity to the new requirement in *Takeda Chemical Industries, Ltd v. Alphapharm*. In *Takeda*, Alphapharma challenged the validity of Takeda's patent on Thiazolidinedione derivates on the grounds of obviousness.[43] Thiazolidinedione compounds (TZDs) are a class of compounds which were first discovered to be useful for the treatment of Type 2 diabetes because they have biological activity against insulin resistance. Claim 2 of the patent referred to pioglitazone, which later became the active ingredient of Takeda's drug ACTOS, which is used to control blood sugar in patients with Type 2 diabetes.[44]

Alphapharm's validity challenge rested on a prior art reference, compound b, which showed a compound that differed from pioglitazone in that the pyridyl ring was substituted with a methyl rather than an ethyl, and that the substitution was at the six position of the ring, rather than at the five position.[45] The district court ruled in favor of Takeda finding that the claims were not obvious because there was no motivation to select compound b as the lead compound for antidiabetic research and that the prior art taught away from its use.[46]



Alphapharm appealed, arguing that the lower court misapplied the holding of *In re Dillon*, which said that the structural similarity between compounds could create a *prima facia* case of obviousness. The Federal Circuit elaborated on the requirements of structural similarity, noting that "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds" but a *prima facie* case of unpatentability required "a showing that the prior art would have suggested making the specific molecular modifications

43. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1354 (Fed. Cir. 2007).

44. *Id.* at 1353–54.

45. *Id*. at 1354.

46. *Id.*

necessary to achieve the claimed invention."[47] The court then restated saying, "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."[48]

Applying this rule to the facts at issue, the court found that Alphapharm had failed to make a showing that compound b would have been selected as a lead compound. The court clarified that by lead compound, Alphapharm was referring to "a compound in the prior art that would be most promising to modify in order to improve upon."[49] The court looked at several prior art references, some of which suggested that compound b was particularly important, and some of which did not. The court found that as a whole, the person of ordinary skill in the art would not have selected compound b as a lead compound.[50] The court went on to note that even if Alphapharm had established the preliminary finding that compound b was a lead compound, there was nothing in the prior art that suggested the modifications of changing the ethyl substituent to the methyl substituent and moving the placement of the substituent.[51]

Subsequent cases cite *Takeda* for the required lead compound analysis; however, commentators have suggested that the true origin of the required showings stems from *Yamanouchi*, where the obviousness challenge was so absurd that the court was merely pointing out in dicta the flawed logic of the challenging party.[52] Dicta or not, the lead compound analysis has taken firm root with several other Federal Circuit cases applying the doctrine and cases at the district court level as well.[53]

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47. *Id.* at 1356 (quoting *In re* Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995)).

48. *Id.* at 1357 (emphasis added).

49. *Id.*

50. *Id.* at 1360.

51. *Id.* at 1361.

52. Vincent Capuano, *Obviousness of Chemical Compounds: The "Lead Compound" Concept*, INTELLECTUAL PROPERTY TODAY, July 2007, at 33.

53. *See* Proctor & Gamble Co. v. Teva Pharm., USA, Inc., 566 F.3d 989 (Fed. Cir. 2009); Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075 (Fed. Cir. 2008); Ortho-McNeil Pharm., Inc. v. Mylan Lab., Inc., 520 F.3d 1358 (Fed. Cir. 2008); Eisai Co. Ltd v. Dr. Reddy Lab., 533 F.3d 1353 (Fed. Cir. 2008); Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999 (Fed. Cir. 2009); Pfizer, Inc. v. Apotex, Inc., 488 F.3d 1377 (Fed. Cir. 2007); Eli Lilly & Co. v. Sicor Pharm., Inc., 705 F. Supp. 2d 971 (S.D. Ind. 2010); Pfizer Inc. v. IVAX Pharm., Inc., No. 07-CV-00174 DMC, 2010 WL 339042 (D.N.J.); Sanofi Aventis Deutschland GMBH v. Glenmark Pharm., Inc., No. 07-CV-5855DMC, 2010 WL 2428561 (D.N.J.); Unigene Lab., Inc. v. Apotex, Inc., No. 06 CV.5571 2009 WL 2762706 (S.D.N.Y.); Eli Lilly & Co. v. Actavis

C. Current Application of the Lead Compound Analysis

Since its development several cases have shed light on the nuances of the lead compound analysis. In its simplest form, in order to find a chemical compound obvious, a party must prove first that a person of ordinary skill would have selected the compound as a lead compound. Second, it must be proved that the person of ordinary skill in the art would have had some motivation to modify the lead compound. Finally, a court will weigh rebuttal evidence. The nuances, as well as some gaps in the doctrine have been shown by subsequent case law where the doctrine has been invoked.[54]

1. Selection of the Lead Compound

The party challenging the obviousness of a chemical composition must first establish a lead compound.[55] The Federal Circuit defined lead compound in *Takeda* as a compound in the prior art that would be "most promising to modify" to obtain better activity.[56] A compound which has been singled out in its field is more likely to be considered to be a lead compound; whereas negative side effects can sway the court against finding that the compound was a lead compound. A party challenging obviousness is more likely to prevail when there are a small number of lead compounds, but is not limited to a single lead compound.[57]

In *Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.*, the Federal Circuit affirmed a district court's determination that a compound was a lead compound because the compound was identified as the most active in the field.[58] The dispute centered around Altana's

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Elizabeth LLC, 676 F.Supp. 2d 352 (D.N.J.); Merck Sharp & Dohme Pharm. v. Teva Pharm. USA, Inc., No. 07-1596 2009 WL 3153316 (D.N.J.); Bayer AG v. Dr. Reddy's Lab., Ltd., 518 F. Supp. 2d. 617 (D. Del. 2007); Daiichi Sankyo Co. Ltd. v. Mylan Pharm., Inc., 670 F. Supp. 2d. 359 (D.N.J.); In re '318 Patent Infringement Litigation, 583 F.3d 1317 (Fed. Cir. 2009); Novartis Pharms. Corp. v. Teva Pharm. USA, Inc., No. 05-CV-1887, 2007 WL 2669338 (D.N.J); Pfizer v. Teva Pharms. USA, Inc., 482 F. Supp. 2d. 390 (D.N.J.); Janssen Pharm. v. Mylan Pharm., Inc., 456 F. Supp. 2d 644 (D.N.J.).

54. *See infra* Section II.

55. Contentions by parties to the contrary have been rejected by courts. In *Bayer AG v. Dr. Reddy's Laboratories*, Dr. Reddy's attempted to argue that it did not need to establish a lead compound and did not have any testimony on the subject. The court disagreed and required a lead compound. 518 F. Supp. 2d 617, 626–27 (D. Del. 2007).

56. *See* Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007).

57. Eisai Co. Ltd v. Dr. Reddy's Lab., Ltd., 533 F.3d 1353 1358–59 (Fed. Cir. 2008).

58. Altana Pharma AG v. Teva Pharms. USA, Inc., 566 F.3d 999, 1008 (Fed. Cir. 2009).

patent on pantoprazole, the active ingredient in, PROTONIX®.[59] Pantoprazole is a proton pump inhibitor (PPI) and was developed after AstraZeneca had successfully marketed another PPI, omeprazole.[60] Teva argued that the patent on pantoprazole was invalid in light of both Altana's own patent disclosing a similar compound, compound 12, and AstraZeneca's patent on omeprazole.[61] The district court found that a person of ordinary skill in the art would have selected compound 12 as a lead compound.[62] The Federal Circuit affirmed, finding that the district court's decision was not clearly erroneous,[63] despite the fact that Altana produced evidence that there were concerns about the toxicity of compound 12, and that there were over ninety other compounds disclosed by the prior art.[64] The district court based its decision on evidence that compound 12 was the natural choice for further development because it had a higher potency than any of the other compounds.[65]

The opposite decision was reached in *Takeda v. Alphapharm* where the parties presented multiple prior art references.[66] Some of the references identified compound 12 as important, while other references identified different compounds as important. The court also found references discussing the side effects of compound 12 noting that "negative properties . . . would have directed one of ordinary skill in the art away from that compound."[67]

The number of potential lead compounds is also important to the lead compound analysis. In *Ortho-McNeil Pharmaceutical v. Mylan*, Mylan challenged Ortho-McNeil's patent on topiramate.[68] Although topiramate's anticonvulsant properties had been discovered by chance while a scientist was looking for a diabetes drug, Mylan argued that a

59. *Id.* at 1002.

60. *Id.* at 1003.

61. *Id.* at 1004–05.

62. *Id.* at 1005.

63. *Id.* at 1010.

64. *Id.* at 1008.

65. *Id.* ("Although 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. It bears mention that Altana itself had selected compound 12 for further development efforts.").

66. Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350 (Fed. Cir. 2007).

67. *Id.* at 1359.

68. Ortho-McNeil Pharm. Inc. v. Mylan Lab., Inc**.,** 520 F.3d 1358, 1361 (Fed. Cir. 2009).

person of ordinary skill in the art of searching for a diabetes drug would have found topiramate. The Federal Circuit disagreed stating that, "[t]he record . . . does not present a finite (and small in the context of the art) number of options." But that an "easily traversed, small and finite number of alternatives . . . might support a conclusion of obviousness."[69]

While a small number of lead compounds can be advantageous in convincing a court that the person of ordinary skill would have selected a lead compound, parties are not limited to only one lead compound. In *Eisai v. Dr. Reddy's Laboratories, Ltd*, Teva, along with Dr. Reddy's, challenged Eisai's patent on rabeprazole, a proton pump inhibitor developed in the wake of the commercial success of omeprazole.[70] Teva's invalidity claim rested on both omeprazole and another compound.[71] After the district court found rabeprazole nonobvious, Teva appealed, arguing that the district court erred in making it choose a single lead compound. The Federal Circuit contended that Teva, not the district court, chose to limit its case to a single lead compound and again noted that the *prima facie* case for non-obviousness was consistent with *KSR*.[72]

2. Motivation to Modify the Lead Compound

Once a lead compound has been established, the party asserting that a chemical compound is obvious must show some motivation to modify the lead compound in a way that results in the compound at issue.[73] The motivation to modify the lead compound can come from an explicit teaching in the prior art, or can be gleaned from the prior art as a whole. As with the selection of the lead compound, the number of possibilities for modification can be important; however, the modification cannot be the result of mere routine testing. Finally, to make the *prima facie* case of obviousness, there must be some reasonable expectation that the modification will work.

Motivation to modify a prior art compound can come from explicit references in the prior art. In *Altana Pharma AG v. Teva Pharmaceuticals*, the Federal Circuit affirmed the district court's finding that articles within the prior art would have led a person to modify the

69. *Id.* at 1364.

70. Eisai Co. v. Dr. Reddy's Lab., Ltd., 533 F.3d 1353, 1360 (Fed. Cir. 2008).

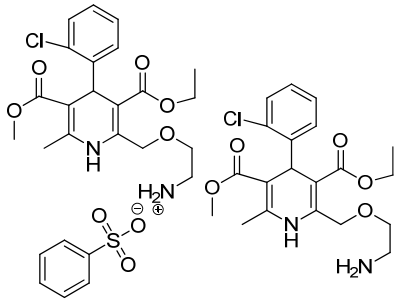
71. *Id.* at 1357.

72. *Id.* at 1358–59.

73. Takeda Chem. Inds., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007).

asserted lead compound.[74] One of the prior art articles suggested that a pKa of 4 would be most desirable for a proton pump inhibitor because it would improve the stability prior to the compounds introduction to the parietal cells in the stomach.[75] Another reference suggested that the specific substitution made in transforming the lead compound, substituting a methoxy group for a methyl group would provide a lower pKa. The Federal circuit found that this evidence supported the district court's finding that a person of ordinary skill in the art would have found the modifications to the lead compound obvious.[76]

Courts have also found motivation to alter the lead compound in the absence of a specific teaching. In *Pfizer v. Apotex*, Apotex challenged the validity of Pfizer's patent on the compound amlodipine besylate.[77] Amlodipine besylate is the besylate salt of amlodipline, a compound which had previously been patented.[78] The prior art also discussed pharmacologically acceptable salts of amlodipine, but never the besylate salt specifically.[79] The Federal Circuit overturned the district court's finding of non-obviousness. The Federal Circuit noted that consistent with *KSR*, motivation could "be gleaned" from the prior art as a whole. There were a limited number of pharmacologically acceptable salts, and besylate was known to have favorable properties; thus, a person of ordinary skill in the art would have found it obvious to modify amlodipine to its beslyate salt.



amlodipine besylate amlodipine

In *Pfizer v. Apotex*, the court also noted that the discovery of the

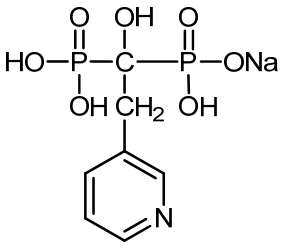
74. Atlana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1008 (Fed. Cir. 2009).
75. *Id.* at 1004.
76. *Id.* at 1010.
77. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1352 (Fed. Cir. 2007).
78. *Id.* at 1353.
79. *Id.* at 1361.

besylate was the product of routine testing and thus did not meet the standards of patentability. While the court noted that in the last sentence of 35 U.S.C. § 103, "[p]atentability shall not be negatived by the manner in which the invention was made,"[80] the court noted that consideration of the "routine testing" by Pfizer was appropriate because it provided both the means and the likely results of trying the compound with acceptable salts.[81] The court likened the choosing of the salt to optimization of a reaction which flows from the "'normal desire of scientists . . . to improve upon what is already . . . known.'"[82]

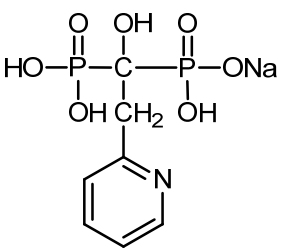
3. Likelihood of Success

Finally, the cases have also established that in addition to the motivation to modify the lead compound, there must be some likelihood of success in modifying the lead compound. A showing that the field was highly unpredictable can weigh against a *prima facie* case.

In *Proctor & Gamble v. Teva Pharmaceuticals*, Teva challenged P & G's patent on the compound risedronate as obvious in light of another patent that disclosed thirty-six other molecules for preventing bone resorption.[83] Teva argued that the structural similarity between risedronate and the prior art compound, 2-pyr EDHP would have made risedronate obvious to a person of ordinary skill in the art.[84]



risedronate



2-pyr EHDP

Risedronate and 2-pry EHDP are positional isomers, differing in the placement of only position. The district court found that 2-pyr-EHDP was not likely to be selected as a lead compound because there were a

80. 35 U.S.C. § 103 (2010).

81. *Pfizer*, 480 F.3d at 1367.

82. *Id.* at 1368.

83. Proctor & Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 993 (Fed. Cir. 2009).

84. *Id.*

number of other compounds disclosed in the '406 patent, and 2-pyr EDHP was not specifically claimed.[85] Other prior art had suggested the concept of testing the positional isomers but the court found that these modifications would not have been obvious in the field of bisphosphonates due to their unpredictability.[86] The Federal Circuit affirmed, while the court noted that a compound may provide the motivation to try its isomer, analog or homolog, in this case there was insufficient evidence for a person of ordinary skill to test risedronate due to the unpredictability of the field.[87] The court concluded that Teva had also failed to show that a person of ordinary skill in the art would have had a reasonable expectation of success in synthesizing risedronate.[88]

In *Pfizer v. Apotex*, the court overturned the district court's finding that a skilled artisan would not have had a reasonable expectation of success in making the besylate salt of amlodipine. Pfizer had presented evidence at the trial that there was no reliable way to predict whether a salt would form and what its exact properties would be. The court noted that "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there is some reasonable probability of success."[89]

A compound's unexpected positive properties can rebut the presumption. In *Sanofi-Synthelabo v. Apotex*, the court found that a patent for a single enantiomer of a lead compound was not obvious because the separation produced unexpected results.[90] The compound at issue in *Sanofi-Synthelabo* was the d-enantiomer of clopidogrel bisulfate. The racemic mixture of clopidogrel had previously been patented by Sanofi-Synthelabo. The court found that the racemate would have been identified as a lead compound by a person of ordinary skill in the art despite problems with its toxicity.[91] Sanofi-Synthelabo decided to undertake the separation of the enantiomers and found absolute stereoselectivity, meaning that the d-enantiomer showed all the favorable therapeutic activity while the l-enantiomer showed all of the

85. Proctor & Gamble Co, v. Teva Pharm. USA, Inc., 536 F. Supp. 2d. 476, 495 (D. Del. 2008).

86. *Id.*

87. *Proctor & Gamble Co.*, 566 F.3d at 995.

88. *Id.* at 996.

89. *Id.* at 1364.

90. Sanofi-Synthelab v. Apotex, 550 F.3d 1075, 1090 (Fed. Cir. 2008).

91. *Id.* at 1080.

toxicity.[92]

Apotex appealed arguing that the district court had applied an incorrect legal standard and should have asked not whether the results were unexpected, but rather, whether or not it would be obvious to try to separate the enantiomers.[93] The Federal Circuit affirmed, noting that a person of ordinary skill would not have expected absolute stereoselectivity.[94]

The opposite result was reached when stereoisomers were separated in the absence of unexpected results. In *Aventis Pharma Deutschland GMBH v. Lupin*, *Ltd.*, a claim to the pure S enantiomer of a ACE inhibitor was found to be obvious.[95] The prior art had disclosed related ACE inhibitors and the fact that the all-S configurations were more potent.[96] The court determined that the patent was obvious.[97]

Finally, if the case of obviousness is sufficiently strong, no rebuttal evidence will be able to overcome it. In *Pfizer v. Apotex*, after finding that a prima facie case of obviousness for amlodipine besylate had been made, the Federal Circuit rejected Pfizer's argument that unexpected results overcame the prima facie case. The court noted that even if Pfizer had presented unexpected results, it would not have overcome the strong case of obviousness.[98]

II. PROBLEMATIC ASPECTS OF LEAD COMPOUND ANALYSIS

The lead compound analysis is problematic in several ways. First, lower courts are often confused by the test, and its limits are not well understood. Second, the test is exactly the type of rigid application that the Supreme Court warned against in *KSR v. Teleflex*. Moreover, the test fails to consider some of the realities of drug development in important aspects such as synthesis.

Several aspects of its application are still problematic even as the lead compound analysis is becoming more solidified in the case law. One main problem with the test is that its limits are not clearly defined by the Federal Circuit and lower courts have applied the doctrine to cases where it is not clear that structural similarity is more at issue or at

92. *Id.* at 1081.

93. *Id.* at 1089.

94. *Id.* at 1087.

95. Aventis Pharma Deutschland GMBH v. Lupin, Ltd., 499 F.3d 1293, 1294–95 (Fed. Cir. 2007).

96. *Id.* at 1296.

97. *Id.* at 1303.

98. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1381 (Fed. Cir. 2007).

least not the only issue. Another problem which has been addressed, but only in a cursory fashion, is whether the lead compound analysis, which is highly rigid and formulaic, comports with the requirements for any obviousness analysis from *KSR*, which is that the approach must be flexible.

A. Application to Combination Drugs

In *Sanofi-Aventis Deutschland GMBH v. Glenmark Pharmaceuticals*, the District Court of New Jersey used the lead compound approach to assess the obviousness of a combination drug.[99] A combination drug, sometimes also called a fixed dose combination, combines two or more pharmaceutical agents in a single drug.[100] Most pharmaceuticals traditionally have only one active ingredient. Combination drugs have become increasingly popular—some because the two drugs work synergistically, also doctors sometimes prefer combination drugs because they increase compliance.[101]

In *Sanofi Aventis Deuschland GMBH v. Glenmark Pharmaceuticals*, Aventis sought to enjoin Glenmark from selling a generic form of Tarka®, a hypertension drug. Tarka® combines trandolapril, immediate release angiotensin converting enzyme inhibitor, and verapamil hydrochloride, a slow release formulation of a calcium channel blocker. Thus, it has two separate components, whose structures are as follows.

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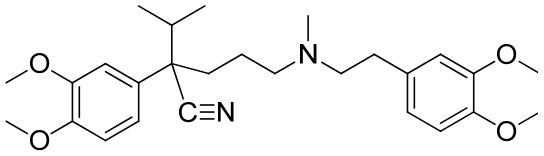
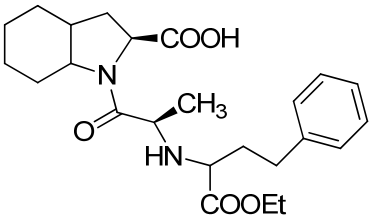
99. Sanofi-Aventis Deutschland GMBH, v. Glenmark Pharm. Inc., USA, No. 07-CD-5855 DMC, 2010 WL 2428561 (D.N.J.).

100. Popular examples of combination therapies include Symbyax® which combines Zyprexia® and Prozac®, and Caduet®, which combines Lipitor® for high cholesterol and Norvasc® for hypertension.

101. *See* Fing Pan et al., *Impact of Fixed-Dose Combination Drugs on Adherence to Prescription Medications*, 23(5) J. Gen. Internal Med., 611 (2008) (discussing the number of medications prescribed as one of many factors affecting patient compliance with a prescribed regimen). For a study of patients views on the benefits of combined pills versus multiple medications see generally B. Williams et al., *Patient Perspectives on multiple medications versus combined pills: a qualitative study*, 98 QJM 885 (2005).



Verpamil



Trandolapril

Sanofi's Patent claimed combinations of an angiotensin-converting inhibiter with calcium agonists in drugs. Angiotensin converting enzyme is an enzyme in the body that mediates, vasoconstriction, by converting angiotensin I to angiotensin II and by degrading bradykinin, a vasodilator.[102] An angiotension converting enzyme agonist is a molecule that binds to the Angiotensin converting enzyme to reduce its activity. Several compounds act as ACE inhibitors,[103] but the patent claimed a two specific ACE inhibitors quinapril and trandolapril. Calcium channel blockers disrupt the flow of Calcium ions in the body. In blood vessels, decreased calcium results in less contraction of the vessels and increase arterial flow. Again, several compounds are known to act as calcium channel blockers and the patent was not restricted to any certain inhibitor.[104]

In assessing Sanofi's request for an injunction, the District Court for New Jersey applied the lead compound analysis in determining the

102. Boron Walter, Ph.D. Medical Physiology, A Cellular and Molecular Approach, 886–87, 1059 (2003).

103. For example, benazepril, captopril, enalapril, fosinapril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril.

104. Sanofi-Aventis Deutschland GMBH, 2010 WL 2428561, at *11. Examples include amlodipine, aranidipine, azelnidipine, barnidipine, benedipine, bepridil, clinidipine, clevidipine, diltazem, fendilinem, isradipine, efonidipine, felodipine, fluspirilene, gallopamil, lacidipine, lercanidipine, manidipine, mibefradil nicardipine, nifedipine, nivadipine, nimodipine, nisolidipine, nitrerdipine, pranidipine, verpamil.

likelihood of success on the merits.[105] In assessing the likelihood of success on the defense of obviousness, the court invoked the lead compound analysis. Citing *Takeda*, the court noted 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."[106] The court then went on to assess the relevant prior art, which included (1) a prior art reference suggesting the ACE inhibitor captopril with a calcium agonist, (2) a different ACE inhibitor, enalapril with a calcium agonist nifedipine, (3) a reference teaching that quinapril was "considerably more potent" than either elanopril or catopril.[107]

The court found that the likelihood of success on the merits favored Glenmark, and that the prior art weighed toward a finding of obviousness. While Sanofi asserted that there were important structural differences between enalapril, quinapril, and captopril,[108] the court rejected this argument, but on the basis that the '244 patent did not purport to resolve the problems of structure or ACE or mechanism of action of the ACE inhibitor.[109] The court also gave little weight to Sanofi's evidence of synergistic effects for the combination, however the court found that those contentions, which included evidence that Tarka® was longer acting, more effective than a separate dosage, more effective in African American patients, and reduced the incidence of cardiac events, more than other compounds, the court did not give this much weight because the embodiment was narrower than the claims of the invention.[110]

B. Application to Formulations

Another questionable application of the lead compound analysis is its application to patents on different chemical formulations. A patent

105. *See id.* at *5 ("In determining whether a preliminary injunction should issue, we apply the four factor test set forth by the Supreme Court. In general, a plaintiff seeking a preliminary injunction must establish [1] that he is likely to succeed on the merits, [2] that he is likely to suffer irreparable harm in the absence of preliminary relief, [3] that the balance of equities tips in his favor, and [4] that an injunction.") (quoting Winter v. NRDC, Inc., 129 S. Ct. 365, 374 (2008)).

106. *Id.* at *8 (quoting Takeda Chem. Ind., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007)).

107. *Id.* at *8–*10.

108. *Id*. at *12.

109. *Id.*

110. *Id.* at *14.

on a chemical formulation is used widely for pharmaceutical patents to describe both the inactive and active ingredients of a drug, along with their relative compositions. Patents on chemical formulations are also prevalent in many other areas not limited to formulations. A formulation patent for a pharmaceutical was at issue in *Unigene Laboratories v. Apotex*.[111] Unigene was the owner of the '392 patent[112] for nasal calitonin formulations. The patent claimed a pharmaceutical composition of calcitonin, citric acid, phenyl ethyl alcohol, benzyl alcohol, and polysorbate in a specified concentration.[113] The patent reported that the concentration conferred unexpected and beneficial properties when administered in that concentration.[114] After Apotex submitted an Abbreviated New Drug Application (ANDA) for a generic of the commercial embodiment of the patent Fortical®, Unigene sued, asserting artificial infringement.[115] Apotex argued that the patent was invalid as obvious and that the claim at issue would have been obvious based upon a large number of prior art teachings.[116] Apotex also asserted that obviousness could be based on a lead compound, Miacalcin, a compound similar to salmon calcitonin which consisted of a formulation including Miacalcin in about the same composition as the patent reported for salmon calcitonin.[117] While ultimately rejecting Apotex's obviousness argument,[118] the court applied the lead compound analysis by concluding that Micalin was a lead compound for the development of similar drugs.[119]

C. Lead Compound Analysis and the Requirements of KSR

Beyond its questionable applications, the lead compound obviousness analysis prompts another important question, that is, does anything warrant this special test after *KSR*? The lead compound analysis began before the Supreme Court cautioned against rigid and inflexible approaches toward obviousness.[120] The Supreme Court's landmark *KSR* decision came down in 2007, but the Federal Circuit

111. Unigene Labs. v. Apotex, No. 06-CV-5572, 2009 WL 2762706 (S.D.N.Y.).
112. U.S. Patent No. 6,440, 392, Issued Aug. 27, 2002.
113. *Id.* at Col 6, l. 35–37.
114. *Id*. at Col. 7, l 20–22.
115. *Unigene Labs.*, 2009 WL 2762706.
116. *Id*. at *7.
117. *Id.*
118. *Id.* at *15.
119. *Id*. at *7 n.11.
120. *See* KSR Int'l Co. v. Teleflex, 550 U.S. 398, 415 (2007).

cases before and after *KSR* show that the Federal Circuit's analysis has changed little after *KSR*.

In *KSR v. Teleflex,* a patent licensee alleged that a competitor infringed the licensed patent for an accelerator pedal assembly for vehicles.[121] Automobile gas pedals control the rate at which gasoline and air enter the engine.[122] In the 1970s, these petals were improved such that the pedal could be adjusted within an automobile's footwell to accommodate small drivers.[123] The prior art included adjustable pedal assemblies where both the pedals and the pivot points moved when the driver adjusted the footwell. Regardless of the adjustability, pedals can interact with the throttle in two ways, either by a mechanical link or by a computer that detects the position of the petal and transmits that information to the throttle electronically.[124] The Rixon patent revealed an adjustable pedal assembly with an electronic sensor mounted in the footpad of each pedal.[125] The wires connecting the electronic sensors to the computer controlled throttle in the Rixon disclosure, however, were known to chafe as a result of the pedal arm's movement.

The patent at issue in *KSR* was the Engelgau patent which improved on the Rixon patent. It disclosed a position-adjustable pedal assembly with an electronic pedal position sensor attached to the support assembly that allowed the sensor to remain in a fixed position while the driver adjusts the pedal.[126] Not knowing of the Engelgau disclosure, General Motors Corporation asked KSR to supply adjustable pedal systems.[127] Teleflex then notified KSR of the Engelgau patent and sought a licensing fee. After negotiaiations broke down, the KSR challenged the patent's validity on grounds of obviousness.[128]

After the district court granted summary judgment in favor of KSR, holding that the patent was invalid as obvious, the Federal Circuit overturned.[129] The Federal Circuit, in overturning the decision noted the powerful attraction of hindsight bias in the obviousness analysis.[130]

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121. Teleflex, Inc. v. KSR Int'l Co., 298 F. Supp. 2d. 581 (E.D. Mich. 2003).

122. Daniel Becker, KSR v. Teleflex: *How "Obviousness" has Changed,* 4 DUKE J. CONST. L. & PP SIDEBAR 45, 46 (2009).

123. *Id.*

124. *Id.* at 46–47.

125. U.S. Patent No. 5,819,593 (filed Aug. 17, 1995).

126. U.S. Patent No. 6,109,241 (filed Jan. 26, 1999).

127. KSR Int'l Co. v. Teleflex, 550 U.S. 398, 410 (2007).

128. Teleflex, Inc. v. KSR Int'l Co., 298 F. Supp. 2d. 581, 587 (E.D. Mich. 2003).

129. Teleflex v. KSR Int'l Co., 119 F. App'x 282, 283 (Fed. Cir. 2005).

130. *Id*. at 288.

The Federal Circuit then noted that the best way to avoid the distortions of hindsight bias was to apply the court's teaching-suggestion-motivation test, which requires a court to make a specific finding of some teaching suggestion or motivation in the prior art to combine previous elements in the way asserted to be obvious.[131]

The Supreme Court disagreed.[132] The Supreme Court disagreed with several aspects of the Federal Court's decision, but the main holding was that the Federal Circuit's obviousness analysis was overly rigid and formulaic, and could not encompass the flexibility needed for an obviousness analysis.[133] In overturning the Federal Circuit's contention that the person of ordinary skill in the art would not have looked to a patent designed to solve a different problem, the court noted that the person of ordinary skill was also a person of ordinary creativity who could look at patents outside of the exact problem the person was trying to solve.

Further, the court repudiated the Federal Circuit's contention that proof that a combination would have been obvious to try could never be sufficient to establish obviousness. To the contrary, the court held that when there are "a finite number of identified, predictable, solutions," a person attempting to solve a problem will likely first try "known options within his or her technical grasp" and that the results obtained from this process, are merely those of "ordinary skill and common sense."[134]

KSR v. Teleflex was immediately recognized as a dramatic change to the obviousness landscape.[135] After *KSR*, the bright line rule was that if there was no teaching, motivation, or suggestion in the prior art hinting at combining elements in the way the patent combined them, that the patent could not be invalidated as obvious. Not only did the Supreme Court abolish the TSM test as the exclusive test for obviousness, the court emphasized that the correct approach to determining nonobviousness could not generally be contained in a rigid formula, rather the test was to be "expansive and flexible."[136] The Court also gave some additional features to the person of ordinary skill in the art. Now the PHOSITA has been given creativity and common sense to further heighten the standard for nonobviousness.

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131. *Id.* at 290.
132. KSR Int'l Co. v. Teleflex, 550 U.S. 398, 415 (2007).
133. *Id.*
134. *Id.*
135. Becker, *supra* note 122, at 55.
136. *KSR Int'l Co.*, 550 U.S. at 415.

Federal Circuit decisions employing the lead compound analysis have alluded to the doctrine's consistency with *KSR*, but that consistency is questionable. For example, the Federal Circuit in *Takeda*, a post-*KSR* case, squared the lead compound analysis with *KSR*'s directive to identify "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."[137] However, a closer look at *KSR* reveals the inconsistency of these two tests: *KSR* did not contain any rule concerning the motivation of the selection of the primary prior art references. This additional hurdle is significant because it forces a party seeking to prove obviousness to demonstrate rationale for the prior art where that same showing would not be required in a mechanical context. Moreover, the statutory interpretation where obviousness means one thing in one situation, and another in a different context is questionable. The Supreme Court has previously warned against applying the same statutory text differently in different cases.[138]

III. TAKEAWAYS

Understanding the nuances of the lead compound analysis and how it is likely to be applied by both the Federal Circuit and by district courts is important both in litigation challenging a patent's nonobviousness of a chemical compound and for creating strong patent portfolios. Furthermore, an understanding of where the lead compound analysis fails to capture the realities of drug discoveries can be useful in creating policies and practices for protecting chemical innovations where the lead compound analysis is unhelpful.

One important take away from the cases is that the lead compound analysis greatly favors the patentee in most situations. A party challenging the obviousness of a chemical compound faces an uphill battle in showing both that there was a structurally similar compound that would have been considered a lead compound, and that there was a motivation to modify the compound.

An important factor to understand for the lead compound analysis is what exactly a lead compound is and is not, as the court's conception is

137. Takeda Chem. Ind., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356–57 (Fed. Cir. 2007) (citing *KSR*, 550 U.S. at 418.).

138. *See* U.S. v. Santos, 553 US 507, 522–23 (2008) ("[T]he meaning of words in a statute cannot change with the statute's application. To hold otherwise, would render every statute a chameleon and would establish within our jurisprudence . . . the dangerous principle that judges can give the same statutory text different meanings in different cases.") (citations and quotation marks omitted).

likely more narrow than a common sense understanding of the term lead compound. While courts have been willing to say that there could be more than one lead compound, courts have generally assumed that there will be a small number in order for the choices to be sufficiently finite. Thus, a party challenging a compound's obviousness is really created with a Hobson's choice. They can assert that the compound is obvious based on several lead compounds, but if they assert too many, the court may decide that the choices were too numerous for any one compound to be considered lead.

While there is no bright line for how many lead compounds there could be, the cases provide some illustrations of where the line may be from cases where courts have found a chemical compound obvious. The court's main consideration in looking at the number of potential leads comes from language in *KSR* that an important consideration for obviousness is when there are a "finite number of identified, predictable solutions."[139] The court has considered a compound lead when there are only a small number of other compounds. In *Altana Pharma v. Teva*, for example, a compound was considered a lead compound when it was disclosed along with eighteen similar compounds.[140] On the other end of the spectrum, when there are thousands of options, the court is unlikely to find a compound to be a lead compound. For example, in *Takeda*, where the prior art reference disclosed millions of compounds including the compound at issue, the compound was not considered a lead compound.[141]

Another important issue for parties considering litigation over a lead compound is when the compound is part of a formulation or a combination drug. Thus far, there has been no clarity offered by the Federal Circuit on whether the lead compound analysis can be used in combination drugs or not or what would be considered the lead compound. The district court cases show that the court may be willing to consider the structural similarity of components of mixtures.[142] Neither of the district court cases paint a clear picture of how the lead compound analysis might be used in conjunction with other elements. For example, even if the prima facie case was met for one component of

139. *KSR Int'l Co.*, 550 U.S. at 421.

140. Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1008 (Fed. Cir. 2007).

141. *Takeda*, 492 F.3d at 1357 (Fed. Cir. 2007)

142. *See, e.g.*, Sanofi-Aventis Deutschland GMBH v. Glenmark Pharms., No. 07-CV-5855 (DMC), 2010 WL 2428561 (D.N.J.); Unigene Labs. v. Apotex, No. 06-CV-5572, 2009 WL 2762706 (S.D.N.Y.).

a mixture, how would that affect the consideration of whether the combination of that element with other elements was met? Will courts consider the structural similarity separately from the combination of elements? Is there any precedent for such a bifurcation in the obviousness analysis? These questions remain unanswered.

Finally, what can be done when the prior art does disclose a lead compound? For drugs that are developed based off a linear approach, patent protection may be available to those who show unexpected results, or teaching away. The lead compound approach seemlingly failse to take into consideration situations where the sythesis is difficult or unavailable. For example, in the case of gemcitibine, gemcitibine was recognized early on as a compound of particular relevance, but due to its functionality, the compound was not tested.[143] The proposals had only failed because the compound proved so difficult to synthesize, and the lead compound analysis does not take this into consideration. Claims to the compound per se compound would be difficult to defend from a challenge under the current application of the lead compound analysis. However, it seems unfitting that the availability of synthetic routes does not seem to be important to the lead compound analysis.

IV. CONCLUSION

Understanding the development and application of the Federal Circuit's lead compound approach is to chemical obviousness is important for both prosecution and litigation practitioners in the chemical arts. Understanding the Federal Circuit's test, and how it has been used can be predictive in evaluating the strength of protection which may be available to claims to a compound per se, and even, to mixtures of componds. Further, in light of KSR, future litigation may focus on whether the analysis is too rigid, and the Federal Circuit's response may be important in the continuing development of the case law on obviousness.

143. Eli Lilly & Co. v. Sicor Pharm., 705 F. Supp. 2d, 971 (S.D. Ind. 2010).