The Lead Compound Analysis for Chemical Obviousness: USPTO v. the Courts

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Over the last several years, the Federal Circuit has imposed certain requirements for whether a prior art compound qualifies as a lead compound for purposes of assessing whether an invention, such as a pharmaceutical, is obvious under the law. These requirements have arguably favored patent owners by focusing the lead compound inquiry on the *most promising* prior art rather than the *closest* prior art.

The same impact, however, does not appear to be felt at the Patent Office, where the closest prior art compounds continue to be the focal point of a chemical obviousness analysis. The forum where a chemical obviousness battle is played out (patent office vs. the courts), therefore, can have a big impact on the results.

CHEMICAL OBVIOUSNESS

The historical approach to analyzing chemical obviousness evolved out of numerous appeals of Patent Office rejections to the courts.[1] This approach was articulated in the Federal Circuit's 1990 *en banc* decision in *In re Dillon*:

> [S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness, and . . . the burden (and opportunity) then falls on an applicant to rebut that *prima facie* case.[2]

Under this approach, a prior art compound qualified as a starting point for a *prima facie* case if it was structurally similar to the claimed compound and the prior art disclosed *any* utility regarding the prior art compound.[3] There was no requirement that the prior art

[1] See Helmuth A. Wegner, *Prima facie* Obviousness of Chemical Compounds, 6 APLA Q. J. 271 (1978). The historical approach is now embodied in Chapter 2100 of the *Manual of Patent Examining Procedure*, which sets forth the standard rules for analyzing chemical claims for obviousness. *Manual of Patent Examining Procedure*, Patent and Trademark Office, U.S. Department of Commerce §§ 2144.08, 2144.09 (9th ed., March 2014).
[2] *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990).
[3] *Id.* at 697; *see also In re Stemniski*, 444 F.2d 581, 586 (C.C.P.A. 1971); M.P.E.P. § 2144.08 (II)(A)(4)(d) ("close structural similarity alone is not sufficient to create a *prima facie* case of obviousness when the reference compounds lack utility, and thus there is no motivation to make related compounds").

compound have the same utility as the claimed compound or that the prior art compound have more beneficial properties than other prior art compounds.[4]

[4] For cases finding *prima facie* obviousness with the disclosure of some minimum utility, see e.g., *In re Hoch*, 428 F.2d 1341 (C.C.P.A. 1970); *In re Albrecht*, 514 F.2d 1385 (C.C.P.A. 1975); *In re Wilder*, 563 F.2d 457 (C.C.P.A. 1977); *In re Wood*, 582 F.2d 638 (C.C.P.A. 1978).

THE LEAD COMPOUND ANALYSIS AT THE FEDERAL CIRCUIT

More recently, the Federal Circuit has applied a so-called *lead compound analysis* (LCA) to determine whether a prior art compound qualifies as a starting point to prove obviousness. Under the LCA, "[a] court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts."[5]

The LCA differs from the *Dillon* approach in a key respect. To qualify as a starting point under the LCA, a prior art compound must have sufficiently attractive properties to motivate one to select that particular compound out of the prior art, thereby eliminating any de facto presumption that a known compound with useful properties is a valid starting point for a *prima facie* case as it was under the *Dillon* approach. Thus, the LCA raises the bar by effectively requiring that a compound possess a greater quantum of useful and relevant properties before qualifying as a lead compound.

A consequence of the LCA is that the determination of whether a known compound constitutes a lead compound depends on its *relative properties* compared to other compounds in the prior art. Thus, under the LCA, courts have found that prior art compounds having beneficial properties nonetheless would not have been selected as lead compounds where the prior art presented other, more attractive lead compound candidates.

Figure 1 provides a snapshot of several Federal Circuit cases where a defendant's asserted lead compound failed to qualify as a lead compound despite possessing some beneficial property. As explained by the Federal Circuit in *Daiichi Sankyo*, "[p]otent and promising activity in the prior art trumps mere structural relationship."[6]

Case	Property of defendant's asserted lead compound	Property of other prior art compound
Yamanouchi[7]	3x greater activity than cimetidine	10x greater activity than cimetidine
Lilly[8]	Non-halogen containing compound active in a test for antipsychotic activity	Halogen-containing compounds described as preferred; benchmark compound clozapine was more active in test for antipsychotic activity
Takeda[9]	Very effective to lower blood glucose and plasma triglycerides, but undesirable effects on body weight and brown fat	Effective to lower blood glucose and plasma triglycerides without reported negative effects
Daiichi Sankyo[10]	2-4x more active than 1st generation ATII antagonists	More potent or better characterized ATII antagonists disclosed

[5] *Otsuka Pharm. Co. Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012).
[6] *Id.*
[7] *Yamanouchi Pharmaceutical. Co., Ltd. v. Danbury Pharmacal., Inc.*, 231 F.3d 1339, 1343-44 (Fed. Cir. 2000).
[8] *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc*., 471 F.3d 1369, 1379 (Fed. Cir. 2006).
[9] *Takeda Chem. Industs., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1360 (Fed. Cir. 2007).
[10] *Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010).

Otsuka	General disclosure of antihistamine and antipsychotic activity; some activity in a mouse jumping model	Compounds with better activity in the mouse jumping model; clozapine and risperidone disclosed as clinically active antipsychotics

Fig. 1: Cases Where Asserted Compound Failed to Qualify as a Lead Compound

In the cases shown in Figure 2, however, courts agreed with a defendant's lead selection argument where the available starting points were few in number and the evidence pointed distinctly in the direction of a structurally similar lead compound. In other words, the most promising prior art compounds were also the closest prior art compounds.

Case	Property of defendant's asserted lead compound	Property of other prior art compound
ICI[11]	Cardioselective β-blocker	Many non-cardioselective β-blockers
Altana[12]	"Cutting edge of PPI development"	Approved drug omeprazole
BMS[13]	Potent antiviral compound actually being used as a lead compound	Two other classes of antiviral agents that had already been thoroughly explored

Fig. 2: Cases Where Asserted Compound Qualified as a Lead Compound

USPTO'S APPLICATION OF THE LEAD COMPOUND ANALYSIS

In Patent Office proceedings, the LCA has not displaced the historical approach to compound obviousness under *Dillon*, but instead has been assimilated into *Dillon*'s framework.[14]

For instance, in *Ex parte Cao*, the Board[15] rejected the contention that the examiner's failure to conduct the LCA required reversal of the obviousness rejection.[16] In the Board's view, the Federal Circuit's *Eisai* case[17] "did not promulgate a per se rule that chemical compounds can only be held obvious if a lead compound is first identified," nor did it "overrule the longstanding principles that . . . one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties."[18] According to the Board,

[11] *Imperial Chem. Inds, PLC v. Danbury Pharmacal, Inc.*, 777 F.Supp. 330, 354 (D. Del. 1991).
[12] *Altana Pharma AG v. Teva Pharma. USA*, 566 F.3d 999, 1008-09 (Fed. Cir. 2009). The *Altana* decision was rendered at the preliminary injunction stage. Notably after a full trial on a different factual record, the district court sided with the patentee that the same asserted leads would not have been selected. *Altana Pharma AG v. KUDCo.*, No. 04-2355, slip op. at 16 (D.N.J. July 15, 2010).
[13] *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc*., No. 2013-1306, slip op. at 4-11 (Fed. Cir. June 12, 2014).
[14] The authors note that, in 2010, the Patent Office published guidance on how to apply the LCA in the examination of claims to chemical inventions. Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex, 75 Fed. Register 53643, 53651-53 (Sept. 1, 2010). The Examination Guidelines have subsequently been incorporated into M.P.E.P. § 2143 (B).
[15] The Board of Patent Appeals and Interferences and the Patent Trial and Appeal Board are referred to collectively as "the Board."
[16] *Ex parte Cao*, No. 2010-00408 at 7 (B.P.A.I. Sept. 21, 2011).
[17] *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd*., 533 F.3d 1353 (Fed. Cir. 2008).
[18] *Ex parte Cao*, No. 2010-00408 at 7-8.

the LCA "is not the exclusive test for compound obviousness," and the evidence was "appropriately examined under the . . . *Dillon* principle as the Examiner applied it."[19]

Recent decisions of the Board also show that the Patent Office is interpreting the term "lead compound" in a way that does not require a greater showing of beneficial properties than was already required under cases like *Stemniski*[20] and *Dillon*. This has allowed the focus of the obviousness inquiry to remain on the closest prior art compounds having some beneficial utility.

Three exemplary opinions by the Board—*Ex parte Jiminez Mayorga*, *Ex parte Gaul*, and *Ex parte Dong*—illustrate that the LCA is not having the same impact at the Patent Office as it is having in the courts. The Patent Office has gone to great lengths to attempt to reconcile the apparent inconsistencies between the historical approach and the LCA, such that the LCA at the Patent Office may not differ significantly from a traditional chemical obviousness analysis.

Ex parte Jimenez Mayorga

In *Ex parte Jimenez Mayorga*, the Board found that a structurally similar prior art compound (Compound 4) qualified as a lead compound, even though the reference cited by the Examiner (Fukui) disclosed more potent, and presumably more attractive compounds.[21] Fukui's Compound 4 was one of 24 compounds having IC_{50} data, with eleven compounds having a more potent IC_{50} and twelve compounds having a less potent IC_{50}.[22]

On the LCA issue, the Appellants cited to *Eisai* and *Takeda*, arguing that the Fukui reference failed to teach one skilled in the art to select Compound 4 as a suitable compound for modification among the dozens of other disclosed compounds.[23] The Appellants argued that the disclosure by Fukui of eleven other compounds having better activity weighed against selecting Compound 4 as a lead compound.[24] The Board, however, agreed with the Examiner "that it would have been obvious for one of ordinary skill in the art to select Fukui's compound 'as a reasonable lead for further modification.'"[25] The Board explained that this conclusion was based upon the fact that Compound 4 was "one of a mere 24 compounds for which IC_{50} data is provided, and it exhibits good activity relative to the other compounds in that small group."[26]

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[19] *Id*. at 8-9.
[20] *In re Stemniski*, 444 F.2d 581, 586 (C.C.P.A. 1971).
[21] *Ex parte Jimenez Mayorga*, No. 2010-012157 (B.P.A.I. Sept. 30, 2011).
[22] *Id*. at 5.
[23] U.S. Appl. No. 10/555,286, Appeal Brief (March 9, 2010), at 21-23.
[24] *Id*. at 22.
[25] *Ex parte Jimenez Mayorga*, No. 2010-012157 at 8.
[26] *Id*.

Ex parte Gaul

Similar to the *Jimenez Mayorga* decision, in *Ex parte Gaul*, the Board found that the disclosure of a more potent compound in the prior art did not constitute a teaching away from the lead compound asserted by the Examiner.[27] The claims at issue in *Gaul* related to a genus of estrogen related receptor (ERR) modulators that encompassed positional isomers of ERR compounds disclosed in a reference to Player.[28] The Examiner rejected the claims on two grounds. The first basis for the rejection was the "well-established" principle that positional isomers are *prima facie* structurally obvious because of the expectation they will possess generally similar properties.[29] As a second basis for rejection, the Examiner found that Example 8 in Player would have been selected as a lead compound based upon its promising biological activity (it had the second best activity relative to other compounds with activity data).[30]

The Appellants, on the other hand, argued that the examiner identified Example 8 as a lead only through the use of improper hindsight because each of the compounds in the vast genus disclosed in Player would qualify as a lead using the examiner's lead selection criteria.[31] Appellants relied on *Takeda* for the proposition that a lead compound is "… the compound that would be most promising to modify in order to improve its activity."[32] According to the Appellants, Example 12 would have been a better lead compound than Example 8, because Example 12 had the most potent activity and Example 8 was "only the second most active compound."[33]

On the lead compound question, the Board characterized the Appellants' reliance on *Takeda* as misplaced in view of the substantially different facts in that case.[34] First, the Board found that, unlike *Takeda*, the low IC_{50} for Example 8 would have suggested it as a lead compound. Additionally, Appellants had not identified any teaching away from Example 8, as was present in *Takeda*. The Board was not persuaded that the existence of an allegedly better lead (Example 12) would have led away from Example 8, because "the ordinary artisan would not have picked just one compound."[35] The Board relied on *Merck & Co. v. Biocraft Labs., Inc*., 874 F.2d 804, 807 (Fed. Cir. 1989), which held that the prior art disclosure of "a multitude of combinations failed to render any particular formulation less obvious."[36] The Board ultimately affirmed the rejection because the close relationship between the claimed and prior art compounds created an expectation that the claimed compounds would have similar properties to those in the prior art.[37]

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[27] *Ex parte Gaul*, No. 2011-008222, 6 (B.P.A.I. Jan. 5, 2012).
[28] *Id*. at 2-3.
[29] U.S. App. No. 12/043,311, Examiner's Answer (Oct. 29, 2010), at 5-6.
[30] *Id*. at 9.
[31] U.S. App. No. 12/043,311, Appeal Brief (Aug. 20, 2010), at 5.
[32] *Id*. at 6.
[33] U.S. App. No. 12/043,311, Reply Brief (Dec. 29, 2010), at 3.
[34] *Ex parte Gaul*, No. 2011-008222, at 5-6.
[35] *Id*. at 6.
[36] *Id*.
[37] *Id*.

Ex parte Dong

In *Ex parte Dong*, the Board concluded that the recent lead compound cases of *Daiichi Sankyo* and *Otsuka* did not mandate that the prior art disclose biological data for a compound to qualify as a lead compound.[38] *Dong* dealt with claims to analogs of glucagon-like peptide-1 (GLP-1) that were rejected as obvious over two references, Dong and Deacon.[39] Dong disclosed a GLP-1 analog, Example 378, which was identical to Appellants' preferred species except for the presence of a glycine at position 8 rather than serine. Deacon taught that substitutions at position 8 of GLP-1 with either glycine or serine improved metabolic stability and that the serine analog had better stability than the glycine analog. Thus, according to the Examiner, Deacon taught the specific substitution of serine at position 8 of the GLP-1 analog of Dong to arrive at Appellants' preferred compound.[40]

The Appellants argued that the references would not have led one skilled in the art to select Example 378 from the 411 specific compounds of Dong as a lead compound. Appellants placed particular emphasis on the breadth of the prior art disclosure and the lack of any biological data that would lead the skilled artisan to specifically select Example 378. Appellants maintained that the Examiner had resorted to the improper use of hindsight by focusing only on the structural similarity between the claimed and prior art compounds. According to the Appellants, under recent Federal Circuit decisions (e.g., *Daiichi Sankyo*), the selection of a lead compound depended on "more than just structural similarity," but also on "the functional properties and limitations of the prior art compounds."[41]

After reviewing the facts and the recent Federal Circuit lead compound cases, the Board concluded that the Examiner had not erred in finding that the ordinary artisan would have selected Example 378 as a lead for further modification.[42] The Board pointed out that Dong taught a general principle that compounds of the invention had the same effect and use as GLP-1 itself and that, accordingly, Dong did not fail "to provide any reason to select any of its exemplified compounds, including Example 378, as a compound suitable for further improvement."[43] Although Dong did not provide specific biological data for any compounds, the Board found that there was no evidence that one skilled in the art would have expected that any of Dong's compounds lacked the disclosed therapeutic properties.[44]

The Board took particular note of *Daiichi Sankyo*, *Otsuka*, and *Takeda* to comment on the application of the legal principles of those cases to its analysis. From *Daiichi Sankyo*, the Board recognized that the Federal Circuit stated that an obviousness analysis "still requires the [claim] challenger to demonstrate . . . that one of ordinary skill in the art

[38] *Ex parte Dong*, No. 2011-010047, at 1 (P.T.A.B. Jan. 28, 2013).
[39] *Id*. at 3.
[40] U.S. App. No. 10/546,303, Examiner's Answer (Feb. 15, 2011), at 4.
[41] U.S. App. No. 10/546,303, Appeal brief (Nov. 19, 2010), at 8.
[42] *Ex parte Dong*, No. 2011-010047, at 8 (P.T.A.B. Jan. 28, 2013).
[43] *Id*. at 6.
[44] *Id*.

would have had reason to select a proposed lead compound or compounds *over other compounds in the prior art*."[45] And from *Otsuka* and *Takeda*, the Board noted the definition of a "lead compound" 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."[46] The Board, however, explained that it was applying the law of these lead compound cases in a way that did not conflict with other settled principles of obviousness jurisprudence:

> We are not persuaded, however, that *Daiichi Sankyo*, *Otsuka*, or other lead compound cases mandate that the only compounds useful for evaluating obviousness are those for which the prior art has provided specific comparative data. In this case, for example, accepting such an interpretation would effectively render Dong unavailable as prior art for determining obviousness, simply because Dong did not provide data comparing the biological properties of its compounds.
>
> Such an outcome conflicts with the well settled broader principle that, when evaluating claims for obviousness, "the prior art as a whole must be considered."
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> . . . Moreover, as noted above, the Federal Circuit has tempered the rigorousness of the lead compound analysis by stating that "the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound . . . ." *Daiichi Sankyo v. Matrix Labs*., 619 F.3d at 1354 (citing *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)).[47]

EVIDENTIARY AND PROCEDURAL CONSIDERATIONS

Application of the LCA at the Patent Office is also shaped by the nature of the evidence presented during patent examination. In each of the three decisions discussed above, the Board resolved the lead compound question on the basis of a single prior art reference. A limited evidentiary record of this sort is perhaps more conducive to a less rigorous application of the LCA than what the Federal Circuit may apply. For example, absent from the Board decisions is any expert opinion evidence that might detract from an examiner's asserted lead or point to other more attractive starting points. We are left to speculate, of course, whether expert declarations on the lead selection issue might have produced different results in these decisions.

The Patent Office also differs from a court procedurally. An examiner plays the dual roles of establishing the *prima facie* case of obviousness and evaluating whether a patent applicant has successfully rebutted it. And the examiner's conclusions in this regard are governed by a preponderance of the evidence standard. In contrast, an alleged infringer must prove obviousness in the courts by clear and convincing evidence, a higher

[45] *Id*. (internal quotations omitted).
[46] *Id*. at 6-7. (internal quotations omitted).
[47] *Ex parte Dong*, No. 2011-010047, at 7.

standard. The importance of the burden of proof in applying the LCA can be seen in *Ex parte Dong*, where the Board simply needed to conclude that the Examiner did not err in the selection of a lead compound. Unlike in litigation, there was no requirement that the Examiner provide clear and convincing evidence on the lead compound selection step.[48]

CONCLUSION

The decisions discussed above show that, at the Patent Office, the LCA has not displaced traditional approaches to analyzing chemical obviousness and that the Board is evaluating what constitutes a "lead compound" on the particular facts before it. This approach has allowed the Board to apply the LCA in a way that attempts to reconcile the LCA with the settled principles of *Dillon* and other established case law. One apparent consequence is that a lesser quantum of useful properties may qualify a compound as a lead compound at the Patent Office, compared to a district court.

The apparently lower bar at the Patent Office on the lead compound question suggests that pharmaceutical compound patents might be more successfully challenged in an Inter Partes Review (IPR) or a Post Grant Review (PGR) than at a district court. At the same time, patentees faced with such a challenge would likely defend by borrowing the successful litigation tactic of introducing expert opinion evidence that shifts the lead compound inquiry away from the closest prior art to the most promising prior art. It remains to be seen, of course, how the LCA would play out in either an IPR or PGR.[49]

The Patent Office's continued reliance on *Dillon* and its application of the LCA have not yet been appealed to the Federal Circuit.[50] In traditional litigation, however, the Federal Circuit has at times characterized the defendants' lead selection arguments based on structural similarity as the product of hindsight bias. Whether the Patent Office would be accorded deference in its reliance on structural similarity and traditional chemical obviousness law remains to be seen. It seems likely, however, that the Federal Circuit will eventually need to reconcile the arguably different applications of the LCA in the courts and at the Patent Office.

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[48] *See e.g.*, *Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010).
[49] For a recent inter partes review involving a lead compound issue, *see Ranbaxy Labs. v. Vertex Pharms., Inc.*, IPR2013-00024 (P.T.A.B. Mar. 5, 2013).
[50] The authors note that *Dillon* was an en banc decision of the Federal Circuit that has not been overruled in any of the lead compound cases.

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