Obviousness of Chemical Compounds: Navigating the Lead Compound Test at the Patent Office

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The outcomes of *inter partes* review petitions and final written decisions have differed dramatically for claims of pharmaceutical patents, compared to other technologies, particularly for obviousness challenges of compound claims. In contrast to a 73% unpatentability rate across all technologies, the Patent Trial and Appeal Board (“PTAB”) has found pharmaceutical claims unpatentable only 35% of the time. Likewise, in its institution decisions, the PTAB has granted 70% of petitions for *inter partes* review, but only 57% of petitions concerning pharmaceutical patents, and only 30% of petitions raising obviousness challenges of chemical compounds.¹

As emphasized by these statistics, alleging obviousness of a chemical compound involves a particularly complex analysis with numerous pitfalls for petitioners and patent owners alike. This article aims to help navigate these pitfalls at the Patent Office, by exploring PTAB opinions, both in appeals from *ex parte* examination and in *inter partes* review proceedings, on *prima facie* obviousness of chemical compounds, focusing on key issues determinative to the PTAB’s decisions.

**Obviousness Of Chemical Compounds Under The Lead Compound Test**

The requirements for *prima facie* obviousness of chemical compounds differ from all other fields of technology. Prior to considering the obviousness of modifying a prior art compound to produce a claimed compound, a challenger must first establish that a person of ordinary skill in the art would have had reason to select the prior art compound as a “lead” for further modification.² This two-step process is referred to as the “lead compound” analysis and, as recently confirmed by the PTAB, does not apply in the predictable arts.³ The lead compound analysis is notoriously difficult to satisfy; in the sixteen years since its articulation in *Yamanouchi Pharmaceutical Co., Ltd. v. Danbury Pharmacal, Inc.*,⁴ the Federal Circuit has only once found a chemical compound claim invalid under the lead compound analysis.⁵ As shown below, despite the lower burden of proof for unpatentability at the Patent Office, satisfaction of the lead compound test remains a significant challenge.⁶

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The PTAB Has Been Unreceptive To Obviousness Arguments That Do Not Follow The Lead Compound Framework

A debate exists as to whether the lead compound analysis is the sole basis for establishing obviousness of chemical compounds, considering the Supreme Court’s rejection in KSR of a “rigid” test for obviousness and the Federal Circuit’s en banc In re Dillon decision, which some argue relied on structural similarity for prima facie obviousness of a chemical compound. Regardless of the merit of this position, the PTAB’s decisions demonstrate that failure to apply the lead compound analysis is fatal to a petition for inter partes review.

In Torrent Pharmaceuticals Ltd. v. Merck Frosst Canada & Co., the PTAB denied institution of an inter partes review, finding that the petitioner failed to provide a reasoned basis why a person of ordinary skill in the art would have selected the cited substituted benzamide compound for further modification. The petitioner relied on prior art references that identified preferred substituents for a benzamide backbone and argued that based on this finite number of options it would have been obvious to arrive at the claimed compound. Following denial of their petition, petitioner filed a request for rehearing, arguing that the PTAB erred in requiring a lead compound analysis for chemical obviousness and that obviousness could be established based on other rationale, such as where a problem was known in the art for which there existed an easily traversed, small and finite number of alternatives solutions.

The Board rejected the petitioner’s argument, stating that:

as the Federal Circuit noted in Eisai, the Supreme Court’s analysis in KSR relied on several assumptions, including “presuppos[ing] that the record up to the time of the invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound.” In discussing this presumption, the court cited Takeda, reiterating 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.” Id. (quoting Takeda, 492 F.3d at 1357).

The PTAB reached a similar result in Apotex Inc. v. Merck & Co., Inc., rejecting the petitioner’s argument that structural similarity alone was sufficient to make a prior art compound a lead compound for obviousness:

[A] patent challenger must provide “some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness,”
independent of the structural similarity. See KSR Int’l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007). Indeed, the Federal Circuit has repeatedly explained so. See e.g., Daiichi Sankyo Co., Ltd. v. Matrix Laboratories, Ltd., 619 F.3d 1346, 1352 (Fed. Cir. 2010) (“Proof of obviousness based on structural similarity requires . . . evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound . . . .”). “Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection.” Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1292 (Fed. Cir. 2012).

The PTAB’s rulings on this issue, however, are not entirely consistent. In Ex Parte Cao, an appeal from ex parte examination concerning the obviousness of a positional isomer, the PTAB found that chemical obviousness does not always require identification of a lead compound. Without explanation as to the selection of the identified prior art compound as a lead, the Examiner concluded that the claimed positional isomer was prima facie obvious. Applicants argued against the rejection on the basis that the Examiner failed to provide any rationale why a person of ordinary skill in the art would have selected the cited prior art compounds as leads, noting that the compounds were an order of magnitude less potent than the reference’s best compound.

In seeming contradiction to its later decisions in TorrentPharm. and Apotex, the PTAB held that:

The Eisai court did not promulgate a per se rule that chemical compounds can only be held obvious if a lead compound is first identified. The court did say that “a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound” in the prior art. Eisai, 533 F.3d at 1359 (emphasis added). However, the court also said “the requisite motivation can come from any number of sources and need not be explicit in the art. Rather, ‘it is sufficient to show that the claimed and prior art compounds possess a ‘sufficiently close relationship ... to create an expectation,’ in light of the totality of the prior art, that the new compound will have 'similar properties' to the old.’” Id. at 1357 (quoting Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007) (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990)). The Eisai court did not overrule the long-standing principles that the Examiner relied on in this case: 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. Wilder, 563 F.2d at 460; Dillon, 919 F.2d at 692; Aventis, 499 F.3d at 1301.
On a whole, the PTAB seems to require the lead compound analysis for obviousness of chemical compounds, particularly in *inter partes* reviews. *Ex Parte Cao*, while notable, appears to be an outlier, or at least limited to positional isomer cases. As such, until the Federal Circuit or Supreme Court rejects the lead compound analysis as the test for obviousness of chemical compounds, parties asserting obviousness should apply the two-step test, and patent owners should attack challenges that fail to do so.

**Selection Of A Lead Compound Depends On The Properties Of The Compound And The Pertinent Prior Art**

Insufficient support for the selection of a lead compound is a common reason why obviousness challenges of chemical compounds fail. The Federal Circuit has stated that the selection of a prior art compound as a lead for further modification “is guided by evidence of the compound’s pertinent properties” known to a person of ordinary skill in the art at the time of invention,\(^1\) to identify a compound that is “a natural choice for further development efforts.”\(^2\) Such “pertinent properties” include positive attributes, such as activity and potency,\(^3\) adverse effects, such as toxicity,\(^4\) and other relevant characteristics, including the existence of other pertinent prior art compounds.\(^5\)

The PTAB has emphasized the persuasiveness of supporting the identification of a lead compound with activity data. In *Mylan Pharmaceuticals Inc. v. Astrazeneca AB*, the PTAB initiated *inter partes* review, stating that “[b]ased on the potency and stability data . . . , we are persuaded on this record that a skilled artisan would have had reason to choose compound 25 as a lead compound.”\(^6\) Even without actual data, statements that a compound exhibits a desired activity may be persuasive. In *Par Pharmaceutical, Inc. v. Novartis*, the PTAB agreed with the petitioner’s selection of a lead compound, where prior art references described the compound as having “potent immunosuppressant activities,” as well as being “particularly intriguing.”\(^7\) In that case, the PTAB rejected arguments that the compound identified in the petition was not a lead compound because it was not the “most promising to modify.”\(^8\)

The absence of activity data may likewise cut against the selection of a lead compound. In *Apo rex v. Merck*, in rejecting the petitioner’s lead compound, the PTAB noted the absence of activity data for the asserted lead compound and found persuasive the patent owner’s identification of alternative prior art compounds, having promising activity data.\(^9\) In *Sawai et al. v. Nissan Chemical*, the PTAB issued a similar decision, rejecting the selection of a lead that was not supported by activity data:
We note that Picard does not disclose any biological or pharmacokinetic data for the Picard Example 3 Compound, and as such, provides no suggestion that this compound has any particular functional activity to suggest that the compound should serve as a lead compound.\(^{27}\)

Accordingly, in selecting a lead compound, the presence of promising activity data is a key consideration for petitioners, and the absence of such data should be raised by patent owners to challenge the selection, particularly if activity data was available for alternative compounds.

**Evidence Supporting Selection Of A Lead Compound Should Be Specific To The Compound**

The PTAB has found general statements concerning a genus of compounds unpersuasive for the selection of a particular species. While a lead compound need not be the single best compound in the prior art,\(^{28}\) it should be specifically identified as a promising candidate for further modification.

In *Apotex v. Merck*, the cited prior art patent disclosed 601 compounds, without providing activity data for any of the compounds.\(^{29}\) In selecting compound number 96 as a lead compound, the petitioner cited statements in the specification that (1) all the disclosed compounds exhibited improved therapeutic effects over the prior art; (2) the substituents of compound 96 were preferred; and (3) compound 96 was identified in a group of preferred compounds. Based on these statements, the petitioner argued that a person of ordinary skill in the art would have been motivated to select any of the 601 compounds for further development and, in particular, compound 96.\(^{30}\) The PTAB found this argument unpersuasive, stating that the prior art “lists over 600 compounds by their chemical names but provides no activity data for any of them. Under such circumstances, Petitioner’s failure to articulate any reason why one of ordinary skill in the art would have selected compound 96 is fatal to its obviousness analysis.”\(^{31}\)

The PTAB reached a similar conclusion in *Ex Parte Foricher*, rejecting the Examiner’s selection of compound 3125 (out of 3980 compounds) as a lead compound, stating that the prior art reference did not provide a reason to select compound 3125, such as promising activity data.\(^{32}\) The PTAB further noted that “[u]nder Daiichi it is possible to have multiple lead compounds, but due to the large number of compounds disclosed in WO ‘096, it would not be reasonable to classify all 3980 exemplified compounds as joint lead compounds.”\(^{33}\)
Similarly, in *Ex parte Caligiuri*, the PTAB reversed a rejection where the prior art failed to point to a particular lead compound:

The Examiner contends that 0477 qualifies a lead compound because it is “is specifically identified in Claim 36 among only 19 other compounds,” and is thus, “an obvious starting point for optimization.” The Examiner identifies no other reason for selecting 0477 from among the thousands of compounds taught by the reference, nor any reason for selecting 0477 from among the 20 listed in claim 36. 34

The genus of Nugiel claim 1 encompasses thousands, if not millions, of possible compounds, and Nugiel claim 35 recites 286 specific compounds within the scope of claim 1. As Appellants point out, the Nugiel specification does not provide functional data for 0477, or otherwise suggest that it provides any benefit or special property as compared to the many other compounds within the scope of the reference’s disclosure. 35

In *Ex parte Dong*, however, the PTAB reached the opposite result, finding claims to a compound obvious based on a structurally similar compound found in Example 378 (out of 411 total Examples), where the prior art did not disclose activity data for any of the compounds. 36

The PTAB rejected the proposition that activity data was necessary to identify a lead compound and stated that “accepting such an interpretation would effectively render [the reference] unavailable as prior art for determining obviousness, simply because [the reference] did not provide data comparing the biological properties of its compounds.” 37 In affirming the lead compound selection, the PTAB also found no evidence that a person of ordinary skill in the art would have ignored or disbelieved the reference’s general teaching of therapeutic efficacy. 38

Despite its contrary result, the impact of *Ex parte Dong* may be minimal. In its request for rehearing, Apotex cited *Ex parte Dong*, as supporting its identification of compound 96 based on the prior art’s general teaching of therapeutic efficacy. The PTAB dismissed the *Ex parte Dong* decision, stating that it was not precedential and distinguishable because the inventors of the prior art reference actually made the cited Example 378. 39 As such, the selection of a lead compound should be supported by evidence specific to the compound, preferably activity data.
Was There A Motivation To Modify The Lead Compound?

After selection of a lead compound, \textit{prima facie} obviousness requires evidence that a person of ordinary skill in the art would have been motivated to modify the lead compound in a manner that would have produced the claimed invention. The PTAB recently found such a motivation to modify persuasive in \textit{Par Pharmaceutical, Inc. v. Novartis AG}. The petitioner cited references that the identified lead compound was known to have low solubility, which would have been understood to limit the bioavailability of the drug. The PTAB agreed that a person of ordinary skill in the art would have sought to modify the compound to improve its solubility.

The motivation to modify need not be the same as the patentee’s motivation that resulted in the claimed compound. In \textit{Ranbaxy Laboratories, Ltd, et al. v. Vertex Pharmaceuticals, Inc.}, the PTAB rejected the patent owner’s arguments that a person of ordinary skill in the art would not have arrived at the claimed compound because the petitioner’s characterization of the problem to be solved “ignores the complexity of the issues facing the skilled artisan…..”:

A different characterization of the problem facing the '989 Patent’s inventors is not persuasive. “[T]he motivation in the prior art to combine the references does not have to be identical to that of the applicant to establish obviousness.” \textit{In re Kemps}, 97 F.3d 1427, 1430 (Fed. Cir. 1996). “As long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor.” \textit{In re Beattie}, 974 F.2d 1309, 1312 (Fed. Cir. 1992); \textit{See KSR Int’l Co. v. Teleflex Inc.}, 550 U.S. 398, 420 (2007) (“[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.”).

A further point for consideration is whether the proposed modification would have been disfavored at the time of invention. In \textit{Esai}, the Court rejected the defendant’s proposed modification that “would have destroyed an advantageous property of the prior art compound.” Similarly, in \textit{Sawai USA, Inc. v. Nissan Chemical Industries, Ltd.}, the PTAB found that a person of ordinary skill in the art would not be motivated to modify the petitioner’s lead compound, where the modifications were expected to reduce activity of the lead compound.
Were The Steps To Modify The Lead Compound Routine And Predictable?

Whether a reasonable expectation of success exists for modifying a lead compound depends on whether the modification was “routine” or “non-routine.” Routine testing is where “a person of ordinary skill is faced with a ‘finite number of identified, predictable solutions’ to a problem and pursues ‘the known options within his or her technical grasp.’” Non-routine testing would be where one of skill in the art could only vary all parameters or try numerous possible choices until the desired result is achieved, because the prior art provides no indication of which parameters are key or which choices are likely to be successful.

In *Sawai USA, Inc. v. Nissan Chemical Industries Ltd.*, the PTAB rejected the petitioner’s proposed modification on the basis that it required more than “routine optimization”:

we are not convinced that the steps needed to go from Kesseler’s monocyclic compounds to a bicyclic compound—such as the compounds disclosed in Picard—would be considered *routine optimization* such that a person of ordinary skill in the art would have had a reasonable expectation of success in improving the activity of Kesseler’s monocyclic compounds. Fusion of the monocyclic ring structure of the Kesseler compounds would have altered significantly the core structure of the Kesseler compounds and expanded greatly the number of variant compounds resulting from the proposed modification.

In *Mylan Pharmaceuticals Inc. v. Nissan Chemical Industries, Ltd.*, the PTAB rejected the petitioner’s proposed modification as constituting an impermissible “obvious to try” situation, where the prior art provides only general guidance with regard to a line of experimentation to pursue issued a similar finding:

We are not convinced that the steps needed to go from fluvastatin ultimately to pitavastatin constituted routine optimization. The process of modifying fluvastatin to pitavastatin would have required a number of chemical alterations, each having a number of possible combinations. Rather, we find that the process of modifying fluvastatin to pitavastatin would have required significant guesswork and variation of a number of parameters to achieve the end result. For example, if we focus on the modification of the isopropyl group to a cyclopropyl group alone, the prior art does not clearly direct a person of ordinary skill in the art to a cyclopropyl group, let alone the placement of a cyclopropyl group at the 2 position of a quinoline ring.
The PTAB has also considered the applicability of teachings from a secondary reference to a lead compound in deciding whether a person of ordinary skill in the art would have had a reasonable expectation of success in making a proposed modification. In *Ranbaxy Laboratories, Ltd and Ranbaxy, Inc. v. Vertex Pharmaceuticals, Inc.*, the PTAB found that a person of ordinary skill in the art would have had a reasonable expectation of success, where the secondary reference discloses a process specific to the lead compound. The PTAB reached the opposite conclusion in *Mylan Pharm. Inc. v. Gilead Sciences, Inc.*, where the teaching in the secondary reference was not “generically applicable” to the lead compound.

**Conclusion**

Despite inconsistencies in opinions from ex parte examination appeals, a strict lead compound framework controls the determination of obviousness of chemical compounds in *inter partes* reviews. The PTAB’s decisions, particularly in *inter partes* reviews, demonstrate the fact-intensive nature of the lead compound analysis and the rigor with which the judges approach it, even at the institution stage where a petition need only show a reasonable likelihood of unpatentability by a preponderance of the evidence. Raising these substantive demands higher, recent rule amendments for *inter partes* review proceedings now permit patent owners to include expert testimony in a preliminary response. In sum, the lead compound analysis imposes heavy burdens on petitioners and patent owners alike, and counsel must be prepared from the outset to set out detailed factual and technical cases, rooted in the properties of relevant prior art compounds and the synthetic steps necessary to prepare the claimed compound.


2. *See Otsuka Pharm. Co., Ltd., v. Sandoz, Inc.*, 678 F.3d 1280, 1291–92 (Fed. Cir. 2012). “Lead compound” refers to “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.” *Id.* at 1291 (citing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). Stated another way, “a lead compound is ‘a natural choice for further development efforts.’” *Id.* (citing *Altana Pharm. AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)).
3. In connection with a patent directed to a mechanical device, the PTAB in *Arctic Cat, Inc. v. Polaris Industries, Inc.*, rejected the patent owner’s arguments that the petitioner was required to demonstrate why a person of ordinary skill in the art would have selected the asserted “lead reference” for modification to produce the claimed device, stating that “Patent Owner only cites cases involving the unpredictable arts, where identification of lead compounds is more critical, whereas the invention at issue here is in the predictable arts.” See IPR2014-01427, Paper 58, 12-13 (PTAB Feb. 4, 2016).


5. See *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014). This case had unique facts, where both parties’ experts agreed that the modifications necessary to convert the prior art compound to the claimed compound would have been obvious. See also Dzwonczyk, M.R. and Shackelford G.S., *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals: Exploring the effect of post-invention evidence of unexpected results on § 103 nonobviousness*, 60(4) AIPPI Japan Magazine (2015). In *Altana Pharm.*, supra, the Federal Circuit found a likelihood of obviousness, applying the lead compound test.

6. In *Mylan Pharm. Inc. v. Astrazeneca AB*, the PTAB ordered Mylan to file a petition reply on its lead compound selection and proposed modifications, and in granting institution, the PTAB spent twelve pages discussing the proposed modifications. IPR2015-01340, Paper 16, 13-25 (PTAB May 2, 2106).


8. *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (“structural 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 that the burden (and opportunity) then falls on an applicant to rebut that *prima facie* case.”)


14. The prior art included a 4-pyridyl group attached at the 4-position of the thiazole, whereas the claimed compound included a 4-pyridyl at the 5 position.

16. *Id.* at 3.

17. *Ex Parte Cao* at 7-8.

18. In *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014), the Federal Circuit rejected arguments that later-discovered toxicity of a lead compound would deter selection of the compound as a lead, because a person of ordinary skill in the art would not have known of the toxicity at the time of invention. Evidence demonstrated to the contrary that medicinal chemists at the time were in fact using the selected prior art compound as a lead compound.

19. *Otsuka*, at 1292.

20. In *Altana*, 566 F.3d at 1008, compound 12 was found to be a lead compound where it was described as an improvement over the prior art and “one of the more potent of the eighteen [disclosed] compounds.” *See also Eli Lilly*, 471 F.3d at 1379; *Yamanouchi*, 231 F.3d at 1345.

21. In *Takeda*, 492 F.3d at 1358, the asserted prior art Compound b was not considered a lead compound because it displayed undesirable physiological side effects.

22. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1363 (Fed. Cir. 2007) (considering the “strength, solubility, and other known chemical characteristics” of a prior art salt forming acid).


25. *Id.* at 14, *citing Otsuka*, 678 F.3d 1293.


28. *Altana Pharm.*, 566 F.3d at 1008 (Fed. Cir. 2009); *see Par Pharm.*, IPR2016-00084, Paper 8, 10.


30. *Id.*

31. *Id.* at 4. (internal citation omitted).

33. Id.


35. Id. (Emphasis in original).


37. Id.


41. Id. at 10-11.

42. Id.


44. *Eisai Co. Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008).


46. Procter & Gamble Co. v. Teva Pharm., Inc. 566 F.3d 989 (Fed. Cir. 2009).

47. Id.

48. Id.


