Is the Tide Turning on Chemical Patent Challenges at the PTAB?

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The so-called "Lead Compound Analysis" is the primary legal framework for assessing chemical obviousness. Despite the USPTO Patent Trial and Appeal Board's (PTAB) initial apparent reluctance to operate under this framework, the PTAB has been faithfully applying the lead compound framework in America Invents Act (AIA) proceedings, leading to largely favorable outcomes for patent owners. But the decisions we have seen from the PTAB in 2021 relating to chemical obviousness might be early indicators that the PTAB is starting to deviate from the lead compound framework, raising the question—are chemical compound claims facing vulnerability in AIA proceedings?

Twenty years ago, the US Court of Appeals for the Federal Circuit articulated a standard for assessing obviousness of chemical compounds—the so-called Lead Compound Analysis (LCA).[1] Under this approach, a person of ordinary skill in the art ("POSA") must have had a reason to select a prior art compound as a "lead," and a reason to modify the prior art compound with a reasonable expectation of success.[2]

To qualify as a "lead" under the LCA, the compound must possess some beneficial property that somehow distinguishes it from other prior art compounds.[3] In contrast, under the historical predecessor to the LCA framework (*In re Dillon*), one could establish *prima facie* obviousness of a claimed compound if it was structurally similar to a prior art compound with an established utility, and if the prior art provided any reason to make the claimed compound.[4] As such, the LCA raised the standard of *prima facie* obvious of a chemical compound from using only structural similarity to inform selection of a starting point for modification to having to show that the prior art compound to be modified exhibits more beneficial properties than other compounds found in the art. And by focusing on the most promising prior art compound rather than the structurally closest prior art compound, the LCA imposed a much higher burden for showing obviousness in chemical arts, arguably benefiting patent owners.

The PTAB was slow to adopt the LCA, continuing to operate under the historical approach to compound obviousness under *Dillon* in *ex parte* appeals.[5] This reluctance from the PTAB to apply the more stringent LCA in pre-AIA *ex parte* cases contributed to early speculation that pharmaceutical compound patents might be successfully challenged in AIA proceedings.

But the prediction proved wrong. From 2012 through 2020, the PTAB faithfully applied a strict LCA framework in post-grant proceedings, routinely rejecting arguments that *any* reason for modifying a structurally similar prior art compound with a stated utility is sufficient to establish a *prima facie* case of obviousness (*i.e.*, the *Dillon* approach).[6] As one panel explained, "*Dillion* [sic] relates to the rejection-and-response regime of patent examination, rather than the adjudicatory process of an *inter partes* review" and "the burden shifting analysis applied in prosecution 'does not apply in the adjudicatory context of an IPR.'"[7] The PTAB's consistent adherence to the lead compound framework in AIA proceedings led to a nearly universal survival of compound claims, maintaining the public's faith in the general strength of chemical compound patents.

But two 2021 PTAB decisions from two separate panels—both declining to apply lead compound analysis as the exclusive test for obviousness—have cast a shadow on the fate of compound patents in this tribunal.

NOF Corporation v. Nektar Therapeutics

NOF challenged claims 1–12 of U.S. Patent No. 9,187,569 B2 ("the '569 patent"), directed to "branched, reactive water soluble polymers useful for conjugating to biologically active molecules," as being obvious over prior art.[8] Notably, when the patent owner invited the PTAB to "apply the lead compound analysis when assessing whether the claimed genus of chemical compounds would have been obvious over the prior art of record," the PTAB turned down the invitation.[9] Briefly, the PTAB "decline[d] to apply the lead compound analysis as the exclusive test for obviousness," looking instead "to the general law of obviousness for guidance."[10] In the PTAB's view, the LCA "is not the only way to demonstrate obviousness of a claimed compound or genus of compounds," and that "any rigid application of the lead compound analysis risks running afoul of the broad, flexible obviousness test set forth by the Supreme Court of the United States in *KSR*."[11] Under this framework, the petitioner prevailed with regard to all but three surviving claims.[12]

To our knowledge, this is the first expressly-articulated refusal by the PTAB to rely on the lead compound framework as the exclusive test in the chemical obviousness arena of the AIA proceedings.[13]

Alzheon Inc. v. Risen (Suzhou) Pharma Tech Co., Ltd.

Alzheon petitioned the PTAB seeking review of US Patent 10,472,323 B2 ("the '323 patent"), arguing that all claims would have been obvious over the prior art.[14] The '323 patent relates to "isotope-enriched 3-amino-1-propanesulfonic acid ('3APS' or 'tramiprosate') and derivatives, compositions thereof, and methods of

using them in therapeutic applications, such as in the prevention and treatment of Alzheimer's disease."[15] The claims of the '323 patent are directed to isotopically-substituted tramiprosate and its derivative L-valyl-3-aminopropanesulfonate ("Val-APS") and, specifically, where deuterium is substituted for hydrogen at the 3-carbon (*e.g.*, "D2-Val-APS").

Tramiprosate—a known drug that was developed as a treatment for Alzheimer's disease—was known to be extensively metabolized *in vivo*. To improve the therapeutic effectiveness of tramiprosate, the art taught the use of prodrugs and derivatives of tramiprosate that will generate tramiprosate *in vivo* after administration to a subject. One such prodrug, Val-APS, was disclosed by Kong to "significantly increase[] the bioavailability (Cmax and AUC) of tramiprosate, compared to administration of tramiprosate alone."[16] Kong further taught "isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass most abundantly found in nature."[17]

Alzheon argued that the only difference between Kong's Val-APS and the claimed D2-Val-APS is the substitution of deuterium for hydrogen at the third carbon, and that it would have been obvious to a person of ordinary skill in the art to substitute deuterium for hydrogen at the third carbon of Val-APS to form D2-Val-APS.[18] The patent owner, invoking the lead compound framework, argued that a person of ordinary skill in the art would not have had a reason to select tramiprosate or Val-APS as a lead compound for development.[19] To this end, the patent owner argued that "the prior art considered tramiprosate to be a failure, and that there were many other drugs that were considered by the art to be more promising than tramiprosate in treating Alzheimer's disease."[20]

In the institution decision, the PTAB found the patent owner's argument that there would have been no reason to consider tramiprosate—a clinically "failed drug"—as a lead compound "largely irrelevant."[21] The PTAB emphasized that "the question before us is whether the claimed compositions are *structurally* obvious over the cited prior art compositions, and not whether they are, or would have been at the time of filing, effective in the treatment of Alzheimer's disease."[22] The PTAB further explained that "the circumstances under which a 'lead compound' obviousness analysis should be employed" involve "a new chemical compound," and such circumstances "do not apply" here because tramiprosate, and its prodrug Val-APS, are not new chemical compounds: "[t]he chemical structure of tramiprosate and Val-APS are unchanged by the substitution of hydrogen isotopes."[23] The PTAB then concluded that in answering a question of whether a deuterated drug is *prima facie* obvious over its non-deuterated isotopolog, "the standard set forth in *In re Dillon* appears to be the closest applicable standard to apply."[24]

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Notably, the only case known to us (not already mentioned here) where the PTAB cancelled chemical compound claims on a theory of obviousness involved isotopically-substituted compounds.[25] The *Alzheon* proceeding also involves an obviousness challenge to isotopically-substituted compound claims, and it will be interesting to follow to see if claims related to known chemical compounds where the modification is an isotopic substitution are emerging as vulnerable in AIA proceedings.

In sum, after a string of LCA patent-favorable decisions in the chemical obviousness space, the PTAB has surprised us this year by its apparent willingness to deviate from the strict application of the lead compound framework in assessing obviousness of compound claims. While it is too early to tell whether the PTAB will continue with this trend, or if the *NOF* and *Alzheon* cases present an anomaly based on their specific facts, one has to wonder if chemical compound claims are becoming more vulnerable to AIA challenges. In any event, both petitioners and patent owners should recognize that the PTAB is becoming more open to taking a more flexible approach to assessing obviousness of chemical compound claims, and both parties should consider making obviousness arguments that are more expansive than just LCA.

1. *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339 (Fed. Cir. 2000).
2. *See, e.g., Otsuka Pharm. Co. Ltd. v. Sandoz Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012); *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed.Cir. 2007).
3. Otsuka Pharm., 678 F.3d at 1292 ("In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties.")
4. 919 F.2d 688, 692 (Fed. Cir. 1990).
5. *See, e.g., Ex parte Cao*, Appeal 2010-004081 (BPAI Sept. 19, 2011); *Ex parte Mayorga*, Appeal 2010-012157 (BPAI Sept. 29, 2011); *Ex parte Gaul*, Appeal 2011-010047, at 6 (BPAI Jan. 28, 2013); *Ex parte Dong*, Appeal 2011-010047, at 6-7 (PTAB Jan. 28, 2013).
6. *See, e.g., Mylan Pharmaceuticals v. Gilead Sciences*, IPR2014-00887 (PTAB Dec. 9, 2014) (Paper 16) (Rehearing Denied; Paper 22); *Torrent Pharms. Ltd. v. Merck Frosst Canada & Co.*, IPR2014-00559, slip op. 7 (PTAB Jan. 7, 2015) (Paper 10) (Petitioner's request for rehearing denied); *Apotex v. Merck Sharp & Dohme*, IPR2015-00419 (PTAB Oct. 27, 2015) (Paper 18) (Rehearing Denied; Paper 22); *Sawai USA, Inc. v. Nissan Chemical Industries*, IPR2015-01647 (PTAB Feb. 4, 2016) (Paper 9); *Mylan Pharmaceuticals v. Astrazeneca AB*, IPR2015-01340 (PTAB Aug. 18, 2017) (Paper 79); *Par Pharmaceuticals v. Novartis AG*, IPR2016-00084 (PTAB June 23, 2017) (Paper 19); *Argentum Pharmaceuticals v. Research Corporations Technologies*, IPR2016-00204 (PTAB May 23, 2016) (Paper 19); *Mylan Pharmaceuticals, Inc. v UCB Pharma GMBH*, IPR2016-00512 (PTAB July 19, 2017) (Paper 37); *Mylan Laboratories Limited v Aventis Pharma*, IPR2016-00627 (PTAB Aug. 23, 2016) (Paper 10) (rehearing denied, Paper 12); *Fustibal v. Bayer healthcare LLC*, IPR2016-01490, (PTAB Feb. 8, 2017) (Paper 9); *Micro Labs v. Santen*, IPR2017-01434 (PTAB Nov. 29, 2017) (Paper 11); *Sawai Inc. v. Astellas Pharma Inc.*, IPR2018-00079 (PTAB May 4, 2018) (Paper 7); *Initiative for Medicines v. Gilead Pharmasset*, IPR2018-00122 (PTAB May 21, 2018) (Paper 10); *SFC Co. v. LG Chem LTD*, IPR2020-00178.
7. *Sawai Inc. v. Astellas Pharma Inc.*, IPR2018-00079 at 14 (Paper 7).
8. *NOF Corporation v. Nektar Therapeutics*, IPR2019-01397, 3 (PTAB Aug. 5, 2021) (Paper 70). The technical details of this case are complex and not relevant to our discussion of the law applied by the Board in assessing obviousness.
9. *Id.* at 10.
10. *Id.* at 11.
11. *Id.*
12. *Id.* at 56-57.
13. Admittedly, the PTAB has not always applied the LCA in chemical AIA cases. For example, the PTAB also did not apply the lead compound analysis in assessing obviousness of a chemical genus in IPR2017-02005. There, the PTAB did not agree with the Petitioner that the modified prior art subgenus would be "almost entirely within the scope of" the claimed genus, and declined to institute trial. *Gilead Sciences v. Regents of the University of Minnesota*, IPR2017-02005, 17 (PTAB May 29, 2020) (Paper 40).
14. *Alzheon Inc. v. Risen (Suzhou) Pharma Tech Co., Ltd.*, IPR2021-00347, 2 (PTAB July 14, 2021) (Paper 10).
15. *Id.* at 3.
16. *Id.* at 10.
17. *Id.*
18. *Id.* at 13.
19. *Id.* at 20.
20. *Id.* at 22.
21. *Id.* at 25.
22. *Id.* at 25-26.
23. *Id.* at 26.
24. *Id.* at 30.
25. *Incyte Corporation v. Concert Pharmaceuticals, Inc.*, IPR2017-01256 (PTAB Apr. 8, 2019) (Paper 119) (request for Director's review pending).