

INTELLECTUAL PROPERTY & *Life Sciences*

Structure Has Little To Do with Structural Obviousness

A new requirement sets the classic analysis on its ear

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Fear not — no knowledge of chemistry required! A recently denied petition for certiorari from a case originating in New Jersey questioned the current method for determining the patentability of molecules. Obviousness had previously been found where there was a high degree of structural similarity between a new molecule and a prior art molecule — they looked alike when drawn. As long as there was a good reason for modifying the prior art and technology for making that modification, courts had found obviousness. Indeed this analysis is an outgrowth of the chemical discovery

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process. To chemists, similarly structured compounds are often expected to have similar properties, and minor structural changes would be obvious unless they produced unpredicted results.

Recently, however, courts have required a reason, apart from structure, to even select a particular molecule, a so-called “lead compound,” as the starting point of the obviousness analysis. This requirement, unique to the obviousness of molecules, sets the classic analysis on its ear.

The Law of Structural Obviousness and Lead Compounds

Once, the law was simply stated: “[O]ne 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.” *In re Wilder*, 563 F.2d 457, 460 (C.C.P.A. 1977). Even the U.S. Court of Appeals for the Federal Circuit seemed to agree: “[I]t 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.” *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007).

These conceptually simple statements, often deceptively complicated to apply, represented the state of the law. But in *Yamanouchi Pharm. Co. v. Danbury Pharmacal*, 231 F.3d 1339 (Fed. Cir. 2000), a new requirement was articulated. Before one could even ask if a structurally similar prior art compound rendered the claims obvious, one now needed to justify starting with that compound. The question was no longer whether the prior art was the closest structural analog, but rather whether there was an additional reason to start with that particular compound.

A number of cases since *Yamanouchi* extended its “lead compound” requirement. In *Eisai Co. v. Dr. Reddy’s Labs*, 533 F.3d 1353, 1358 (Fed. Cir. 2008), the claimed molecule was found unobvious — not because of a lack of structural simi-

larity or motivation to make the proposed modification, but because the most structurally similar compound of record was not an available starting point. The court stated that “[t]he record, however, shows no discernible reason for a skilled artisan to begin with [the prior art molecule] only to drop the very feature ... that gave this advantageous property.” Similarly, in *Takeda Chemical Industries v. Alphapharm Pty.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007), the Federal Circuit acknowledged that a “known compound may suggest its homolog, analog, or isomer because such compounds often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.” But the court’s remaining discussion had nothing at all to do with this standard and little to do with a comparison of structure.

In *Eli Lilly & Co. v. Zenith Goldline Pharm.*, 471 F.3d 1369 (Fed. Cir. 2006), the full impact of the lead compound concept was revealed. The claimed compound was the next adjacent homolog of a prior art compound — perhaps the simplest and most reasonably predictable analog; think of two strings of identical pearls that differ only in that one string is one pearl shorter. They are not identical, but one would not expect their properties to differ greatly. Difficult as it is to imagine a structurally better place to start, the Federal Circuit simply held that “the defendants [had] not shown that a person ordinarily skilled in this art would have selected [the homolog] as the lead compound” (Note: One of the authors represented the appellant in this appeal.)

In a case originating in this district, the Federal Circuit recently recast the test controlling the obviousness of a claimed chemical compound in *Otsuka v. Sandoz*, 678 F.3d 1280 (Fed. Cir. 2012), cert. denied, No. 12571, 2013 WL 141191 (Jan. 14, 2013). The first prong requires that a “chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development.” 678 F.3d at 1284. Such a lead compound, as defined by the Federal Circuit, is a prior art compound in a given reference that would have shown the most promise, if modified to improve its “activity and obtain a compound with better activity.” 678 F.3d at 1291 (citing

Takeda, 492 F.3d at 1357).

The second prong asks whether or not, based on the prior art, one of ordinary skill in the art would have been motivated to alter the lead compound to make the claimed compound. Such a modification would require a “reasonable expectation of success.” 678 F.3d at 1292.

The patent at issue in *Otsuka* claimed the antipsychotic drug Abilify®. The defendants argued that three structurally similar compounds were acceptable lead compounds, based in large part on their structural similarity to the claimed compound. The Federal Circuit (and the District Court of New Jersey before it) rejected this argument. The court made it clear that structural similarity alone — absent a teaching that the prior art compound had antipsychotic properties — is not enough to establish that compound as a “lead compound.”

The court in *Otsuka* reasoned that the three compounds the defendants advocated were not marketed or known to have “potent antipsychotic activity with minimal side effects.” In its analysis, the Federal Circuit pointed to the evidence offered by the defendants, none of which (according to the court) taught that these compounds exhibited strong antipsychotic properties. Accordingly, the court held that these compounds were not acceptable lead compounds.

Why the Lead Compound Requirement Is Wrong

So why is the lead compound concept wrong? How much time do you have? First, no other area of patent law has a similar requirement. Prior art to a claimed gear is selected because it is structurally similar to the gear claimed — their shapes look alike. Nobody asks why else that gear was chosen from amongst all the known gears as the place to begin. Structural similarity and presumed functional similarity are their own justification. But because of the lead compound requirement, structurally close analogs are now found to be inappropriate starting points, absent more. It is ironic that the entire premise of structural obviousness is that structure creates a *presumption* of similar properties, and that the lead compound concept forces a priori establishment of such properties before that prior art structure can be considered.

Second, the “lead compound” theory

all but eliminates structure from the analysis. In *Otsuka*, the court focused on two compounds suggested by the patentee as possible lead compounds because they were the most promising antipsychotic compounds at the time the inventors began their work. But these compounds, unlike those advocated by the defendants, were not even in the same structural families as the claimed compound; one heck of a misdirection. *Petition for Cert., Otsuka, v. Sandoz*, 2012 WL 5451437 at *6 (Nov. 5, 2012) (No. 12571).

Third, if a prior art reference discloses 50 compounds, yet it identifies one as preferred, and that is the only compound to make it to the market, are the other 49 no longer useful as prior art at all? According to the “lead compound” theory, the answer must be yes. A lead compound presupposes that it is improper to start an obviousness argument from a nonpreferred starting point. Yet, an established body of case law holds just the opposite: “[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention.” *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). In *Merck v. Biocraft Labs*, 874 F.2d 804, 807 (Fed. Cir. 1989), the Federal Circuit explained:

The description of specific preferences in connection with a generic formula, is determinative in an analysis of anticipation under 35 U.S.C. § 102. But in a section 103 inquiry, the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.

(Citations omitted.) See also *In re Gurley*, 27 F.3d 551 (Fed. Cir. 1994). The lead compound theory is in direct contradiction with such precedent. And it is in direct conflict with scientific method — scientists learn from failures in the real world, but apparently not when patenting compounds.

Fourth, in its petition for certiorari, the appellant articulated a telling statistic:

The Federal Circuit’s use of the “lead compound” concept

has had enormous impact on patent litigation; in the twenty-four months following this Court's decision in *KSR*, the Federal Circuit held 33% of the nondrug related patents nonobvious, but in that same period, it held 62% of the drug related patents nonobvious.

Petition, 2012 WL 5451437, at *23.

Conversely, the lead compound

approach should make it easier to get patents on chemical compounds. An examiner would presumably have to identify a lead compound in a rejection. Thus, while the rest of the patent world struggles with enhanced obviousness standards, claiming and protecting molecules should be easier.

That the court in *Otsuka* found no reasonable expectation that the prior art compounds would have antipsychotic properties is reason enough to hold as it did. There might be little reason to sup-

port presumptions of similar properties in a given case or there might be reasons to rebut those presumptions. There might be no reason or motive to change a prior art molecule to arrive at the claimed compound. These are all perfectly valid reasons to reach the court's ultimate conclusion. Disqualifying a structurally similar compound as a starting point per se, however, is not. For now, shackled with a requirement for a lead compound, structural obviousness is more ironic than descriptive. ■