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'Lead Compound' Rule For Drug Patents Leads Courts Astray

By **Roy Wepner** (October 6, 2023, 3:14 PM EDT)


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In patent litigation involving most technologies, the procedure for invalidating a patent for obviousness under Title 35 of the U.S. Code, Section 103(a), is straightforward.

For example, with a patent on a mechanical device, the challenger must first find a prior art device that includes some, but typically not all, features of the claimed invention. The challenger must then prove that it would have been obvious to a person of ordinary skill in that art to modify the prior art device in a way that yields the claimed invention.

But for several years now, patent challengers in the chemical and pharmaceutical arts have faced an added impediment.

Where the patent-in-suit is on a chemical compound, finding a prior art compound that is closely similar to the patented compound is not enough to pursue an obviousness defense. The challenger must first establish that the closely similar compound is a "lead" compound, i.e., a compound that a skilled artisan would have selected as a starting point for developing new compounds.

In this author's opinion, the "lead compound" rule is legally wrong. It finds no support in the patent code. It contravenes several decisions of the U.S. Supreme Court. And it is antithetical to the public policy that supports challenges to invalid patents and to the Hatch-Waxman Act's rationale of making generic drugs more quickly available.

The Lead Compound Rule

By way of illustration, consider Otsuka Pharmaceutical Co. Ltd. v. Sandoz Inc.,[1] a 2012 case involving an effort to market a generic substitute for the drug Abilify. As the U.S. Court of Appeals for the Federal Circuit explained:

> Our case law demonstrates that whether a new chemical compound would have been prima facie obvious over particular prior art compounds ordinarily follows a two-part inquiry. First, the 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.[2]

It further noted that a lead compound is "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," i.e., "a natural

choice for further development efforts."[3] The defendant Sandoz had advanced three compounds as lead compounds. The court rejected all of them.

Factors considered by the Federal Circuit in evaluating a candidate for lead compound include properties such as activity, potency and solubility,[4] and the presence or absence of side effects.[5] Courts consider and weigh expert testimony on the lead compound issue, and the challenger of the patent must justify its selection of a lead compound over other prior art compounds in the mix by clear and convincing evidence.[6]

All that said, however, the prior art compound that is most structurally similar to the patented compound is not necessarily an appropriate lead compound. An obviousness defense based on the most structurally similar prior art compound is often more likely to succeed than one in which there are further differences between the reference and the claimed invention.

But in Daiichi Sankyo Co. Ltd. v. Matrix Laboratories Ltd., the court in 2010 rejected a group of compounds that the defendant characterized as "undisputedly the closest prior art."[7] The court held that "proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds. … Potent and promising activity in the prior art trumps mere structural relationships."[8]

Determination of the appropriate lead compound is often as contentious as determining the actual obviousness of the claimed invention over that lead compound. It is hardly surprising that owners of pharmaceutical patents would pour great resources into advancing as a lead compound one for which proving obviousness is difficult, if not impossible: If a patentee can scuttle a challenger's choice of lead compound, the obviousness challenge has failed — period. For all practical purposes, a compound that is rejected for lead compound status ceases to exist as prior art.

The Legal Deficiencies of the Lead Compound Rule

We begin with the statute:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.[9]

To be sure, while the statute refers to "the prior art," nothing in the statute would suggest discrimination between "lead" prior art compounds in "the prior art" and other compounds in "the prior art." It is equally clear that nothing in the statute suggests that an obviousness analysis for inventions in the chemical and pharmaceutical arts should differ materially from the analysis used in other technologies.

We turn next to pronouncements by the U.S. Supreme Court in patent cases to see if anything in its jurisprudence justifies the lead compound rule. We begin with Graham v. John Deere Co.,[10] which in 1966 provided the patent system with a protocol for determining obviousness that has been a mantra for over half a century:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent

> art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.[11]

Consider first Graham's reference to "the scope and content of the prior art." There is no suggestion here of segregating prior art into items that are deemed preferable or "lead," and thus eligible for an obviousness challenge, and those that are not. The "scope and content of the prior art" would seem to mean what it says: all of the relevant prior art. Likewise, the reference to the "differences between the prior art and the claims at issue" would seem to be inclusive of any relevant prior art.

Perhaps more probative on the present issue is this statement by the Graham court that preceded the familiar mantra: "Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available."[12]

If a prior art compound that is structurally and closely similar to a later-patented compound cannot be the basis for an obviousness defense, one may ask: Does this amount to a restriction on the free access to materials already available?

One response may be that access to the public domain compound itself is not being restricted; only access to an obvious variation on that compound.

But consider a later Supreme Court decision. Bonito Boats Inc. v. Thunder Craft Boats Inc.[13] was not an obviousness case. It involved federal preemption of a state law prohibiting duplication of unpatented boat hulls. But in discussing the policies behind the patent laws, the court in 1989 explained:

> The nonobviousness requirement extends the field of unpatentable material beyond that which is known to the public under § 102, to include that which could readily be deduced from publicly available material by a person of ordinary skill in the pertinent field of endeavor. ... Taken together, the novelty and nonobviousness requirements express a congressional determination that the purposes behind the Patent Clause are best served by free competition and exploitation of that which is either already available to the public, or that which may be readily discerned from publicly available material.[14]

Accordingly, the concerns expressed in Graham about restricting "free access to materials already available" includes not just prior art compounds themselves, but also obvious variants of those compounds — all of them. By kicking to the curb prior art compounds that are not deemed to be lead compounds, courts are effectively preventing "free competition and exploitation" of technology that "may be readily discerned from publicly available material" — i.e., obvious variants on non-lead prior art compounds.

One more Supreme Court decision merits consideration here. In KSR International Co. v. Teleflex Inc.,[15] the court in 2007 struck down another rule erected by the Federal Circuit for obviousness cases.

The Federal Circuit had held that a patent challenger must demonstrate a "teaching, suggestion, or motivation" to combine the teachings of the prior art that had to come from the prior art itself, the nature of the problem, or the knowledge of a person of ordinary skill.[16] While acknowledging that the TSM test captures a helpful insight, the Supreme Court ruled that

> Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. ... [W]hen a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs.[17]

That is precisely what the Federal Circuit has done here. Whatever helpful insights the notion of a lead compound may offer, the court has created a rigid rule for chemical and pharmaceutical cases under which a challenger must first convince the trier of fact that it is relying on a lead compound before the court will even consider whether the patented invention would have been obvious in light of that prior art compound.

Ironically, the Federal Circuit has invoked KSR to prevent litigants from erecting rigid formulas in adjudicating the lead compound issue.[18][19] It is ironic because the entire lead compound requirement itself is precisely the type of rigid rule that KSR prohibits.

Public Policy Is Disserved by the Lead Compound Rule

In U.S. v. Singer Manufacturing Co., the Supreme Court in 1963 said that "public policy favors the exposure of invalid patent monopolies before the courts in order to free the public from their effects."[20]

Moreover, the pharmaceutical arena is a uniquely inappropriate niche in which to erect such an added burden. In enacting the Hatch-Waxman Act, Congress aimed to make cheaper, generic drugs available to patients quickly.[21] Most pharmaceutical patent litigation consists of efforts by generic drug companies to offer such low-cost substitutes. The lead compound rule is a roadblock to the achievement of that goal.

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[1] Otsuka Pharmaceutical Co. Ltd. v. Sandoz Inc., 678 F. 3d 1280 (Fed. Cir 2012).

[2] Id. at 1291.

[3] Id.

[4] See Otsuka, 678 F. 3d at 1292.

[5] See Takeda Chem. Indus. Ltd v. Alphapharma Pty Ltd, 492 F. 3d 1350, 1358 (Fed. Cir. 2007).

[6] Daiichi Sankyo Co., Ltd v. Matrix Labs, Ltd., 619 F. 3d 1346, 1354 (Fed. Cir. 2010).

[7] Daiichi Sankyo, 619 F. 3d at 1364.

[8] Id.

[9] 35 U.S.C. §103 (a) (2013). The current version of Section 103(a) differs in certain respects from the version in effect when many of the cases discussed herein were decided. Such differences are not believed to be material to the matters here discussed.

[10] Graham v. John Deere Co., 383 U.S. 1 (1966).

[11] Id. at 17-18.

[12] Id. at 6.

[13] 489 U.S. 141 (1989).

[14] Id. at 150.

[15] KSR International Co. v. Teleflex Inc., 550 U.S. 398 (2007).

[16] Id. at 407.

[17] Id. at 419.

[18] Daiichi Sankyo, 619 F. 3d at 1352 ("In keeping with the flexible nature of the inquiry after KSR…, the motivation to select and modify a lead compound need not be explicit in the art").

[19] Altana Pharma AG v. Teva Pharms. USA, Inc., 566 F. 3d 999, 1008 (Fed. Cir. 2009) ("[T]o the extent Altana suggests that the prior art must point to only a single lead compound for further development efforts, that restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in KSR.").

[20] United States v. Singer Mfg. Co., 374 U.S. 194 n. 9 (1963).

[21] Andrx Pharms., Inc. v. Biovail Corp. Int'l, 256 F. 3d 799, 809 (D. C. Cir. 2001) ("Congress sought to get generic drugs into the hands of patients at reasonable prices — fast.").