
**A White Paper**

*Prepared and Reviewed by Pharmaceutical Issues Committee*

# LEAD COMPOUND ANALYSIS POST-KSR

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This paper has been prepared by the Intellectual Property Owners Association Pharmaceutical Issues Committee to provide background to IPO members regarding the doctrine of lead compound analysis. It should not be construed as providing legal advice or as representing the views of IPO.

## Introduction

Following *KSR*, which rejected the rigid framework approach by courts to finding motivation in an obviousness inquiry, a question arose - whether or not the existing lead compound analysis framework for determining whether a compound *per se* claim is obvious is still applicable. Based on our findings presented below, courts after KSR continue to apply this framework to compound claims directed toward new chemical entities finding such compound claims to be valid where these claims have been fully litigated.

We analyze in detail the status of the lead compound analysis in several pharmaceutical cases that were decided by the courts post-*KSR*, including four panel decisions by the Federal Circuit in *Eisai, Takeda*, *Altana* and *Proctor & Gamble* and two district court decisions in *Daiichi Sankyo* and *Novartis*.

## Pre-*KSR*

Courts generally adopted the so-called "lead compound analysis" when addressing the question of obviousness of a chemical compound. The term "lead compound" for example refers to a "compound in the prior art that would be most promising to modify in order to improve upon its [] activity and a compound with a better activity" so as to perform further research, development and investigation. *Takeda Chemical Industries v. Alphapharm Party*, 492 F.3d 1350 (Fed. Cir. 2007).

The Federal Circuit stressed that "a prima facie case of obvious requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claim compositions.'" *Eli Lilly v. Zenith Goldline Pharmaceuticals Inc.* 471 F. 3d 1369, 1377 (Fed. Cir. 2006) (quoting *In re Dillon* 919 F.2d 688, 692 (Fed. Cir. 1990)(*en banc*). Specifically, this analysis required motivation to select a lead compound followed by motivation to modify that compound in a particular way in order to arrive at the claimed compound. *Id.* at 1378. Generally, the Federal Circuit required this motivation – also referred to as the teaching-suggestion-motivation (TSM) – to be explicit in the prior art.

## *KSR*

The Supreme Court in *KSR* rejected the long-term application by the Federal Circuit of a rigid TSM test as part of an obviousness determination. *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). The Court stated:

> The analysis need not seek out precise teachings directed to specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

*Id.* at 418.

As part of its more flexible approach, the Court also reversed the long standing rule that "obvious to try" could not constitute obviousness. *Id.* at 421. *See In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995)("[o]bvious to try has long been held not to constitute obviousness"). The Court explained its rationale for adopting, in certain circumstances, an "obvious to try" standard:

> When there is a design need or market pressure to solve a problem and there are a finite number of indentified, predictable solutions, a person of ordinary skill has good reasons to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

*Id.* at 421.

The application of this new flexible approach to "obvious to try" by the courts and its consequences on inventive activity in the pharmaceutical industry is yet to be fully understood, although precedence is starting to evolve in one particular area of subject matter – lead compounds - that may give the practitioner guidance for a post-KSR analysis.

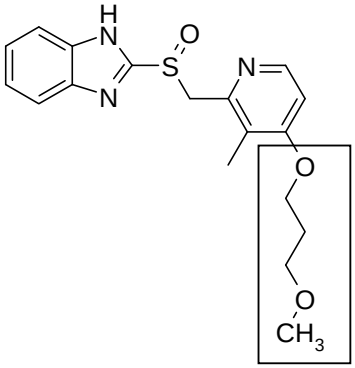
## Post-*KSR*

*Eisai*

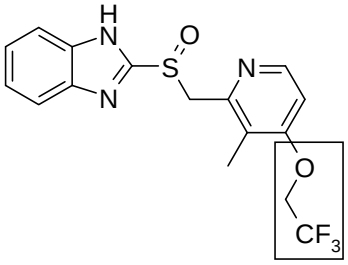
In *Eisai*, the patent at issue claimed the chemical compound rabeprazole and its salts, of which the sodium salt is the active ingredient in Aciphex. *Eisai Co. Ltd., v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008). Aciphex, approved in 1991, is a proton pump inhibitor that treats duodenal ulcers and heartburn. The patent challenger identified lansoprazole as its lead candidate from a prior art reference that disclosed a broad class of gastric acid inhibiting compounds, including omeprazole (Prilosec). The panel pointed out that it is not necessary for the challenger to "rigidly limit" its obviousness arguments to only one lead compound. In this case, the challenger however anchored its obviousness theory to a single compound lansoprazole. Id. at 1358-1359.

Lansoprazole differs structurally from rabeprazole only at the 4-position on the pyridine ring, whereby lansoprazole has a trifluoroethoxy substituent and rabeprazole has a methoxy-propoxy substituent. *Id.* at 1358-59.

Rabeprazole



Lansoprazole



The Federal Circuit panel consisting of Judges Rader, Linn, and Prost, with Judge Rader authoring the opinion, in its discussion of obviousness of rabeprazole applied the holding in KSR and, in doing so, advanced a three-part framework comprised of several assumptions about the prior art relied upon.

> First, KSR assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions.
>
> Second, KSR presupposes that the record up to the time of 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. ("Thus, 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.")(*Takeda*, 492 F.3d at 1357).
>
> Third, the Supreme Court's analysis in KSR presumes that the record before the time of the invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions….To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.
> *Id*. at 1359.

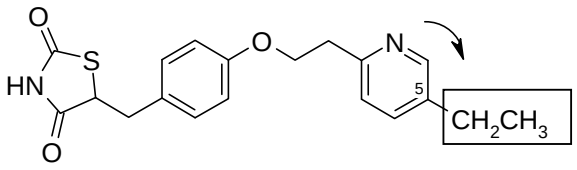
Based on this framework, the Federal Circuit noted that post-KSR, "a prima facie case of obviousness for a chemical compound still, in general, begins

with the reasoned identification of a lead compound." *Id.* at 1359. Having acknowledged the identification of a lead compound, the court in *Eisai* considered the second step, *i.e.*, modification of the lead compound, by replacing the trifluoroethoxy substituent at the 4-position with a methoxypropoxy substituent in order to arrive at rabeprazole. But, the court noted that the reference describing lansoprazole also explained that the fluorinated substituent resulted an increased ability to cross lipid membranes, which was considered a desirable physical property. Thus, the court concluded the "record contains no reasons a skilled artisan would have considered modification of lansoprazole by removing the lipophilicity-conferring fluorinated substituent as an identifiable, predictable solution." *Id*. at 1359. Accordingly, it affirmed the lower court's summary judgment finding of validity.

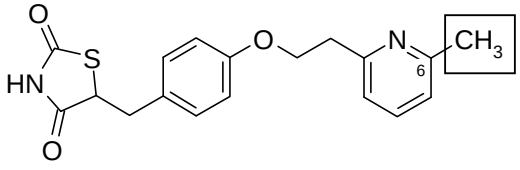
*Takeda*

The patent-at-issue claims the chemical compound pioglitazone, a thiazolidinedione, which is the active ingredient in the drug known as ACTOS, a Type 2 diabetes treatment launched in 1999. *Takeda Chemical Industries, Ltd. V. Alphapharm Pty. Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). The challenger identified prior art "compound b" as its lead compound. The portion of the molecules of interest is the right moiety having the substituted pyridyl ring.

Pioglitazone




Compound b




The patent challenger argued that it would have been obvious to try homologation (changing the methyl substituent to an ethyl substituent) and ring-walking (moving the ethyl substituent from the 6 position to the 5 position). *Id.* at 1359. The Federal Circuit panel consisting of Judges Lourie, Bryson and Dyk disagreed and rejected Alphapharm's assertion that this would have been obvious to try. Based on the prior art as a whole, including a scientific article the court identified as exhaustive and reliable which disclosed undesirable side effects associated with compound b, the court held that one skilled in the art would not have selected compound b as a lead compound for antidiabetic research, stating:

> Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was 'obvious to try.' The evidence showed that it was not obvious to try.
>
> *Id.*

The court further stated:

> Here the court found nothing in the prior art to narrow the possibilities of a lead compound to compound b. In contrast, the court found that one of ordinary skill in the art would have chosen one of the many compounds disclosed in [the prior art reference], of which there were over ninety, that 'did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, rather than to choose as a starting point a compound with identified adverse effects.
>
> *Id.* at 1360.

The court nevertheless continued its analysis assuming that compound b was a valid lead, and considered whether there would have been motivation to modify compound b to form pioglitazone. Alphapharm argued that one skilled in the art would have made the two obvious chemical changes: homologation and ring-walking. *Id.* at 1357. Regarding the allegedly obvious step of homologation, the district court found nothing in the prior art that would have given a reasonable expectation of success for improving compound b's side effects by replacing a methyl with an ethyl. Thus, "researchers would have been inclined 'to focus research efforts elsewhere.'" *Id.* The district court similarly concluded that nothing in the prior art provided a reasonable expectation that ring walking would improve the properties of compound b. *Id.* at 1361.

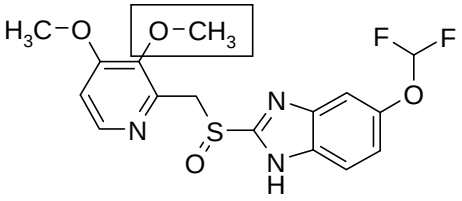
The Federal Circuit found no error in the district court's analysis. *Id.* at 1362. Rather, the court concluded that Alphapharm not only failed to identify a valid lead compound but also failed to show a reason that existed at the time of the invention to chemically modify the assumed lead compound to achieve

pioglitazone. *Id. at 1363*. Accordingly, the court affirmed the lower court's bench ruling that the patent was not invalid.

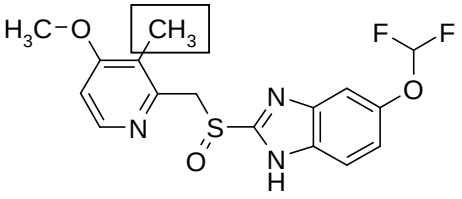
*Altana*

The challenged patent was directed toward the compound pantoprazole, which is the active ingredient in the anti-ulcer drug Protonix®, a proton pump inhibitor. *Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999 (Fed. Cir. 2009). Altana filed a motion for preliminary injunction. Teva and Sun conceded infringement, but alleged that the patent was obvious over four prior art references. Specifically, they identified "compound 12" from the prior art as a lead compound.

Pantoprazole



Compound 12



The Federal Circuit panel of Circuit Judges Newman and Gajarsa, and District Judge Ward, who authored the opinion, agreed that Teva had demonstrated a substantial question of invalidity. The court first noted that "[o]bviousness based on structural similarity may be proven by the identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound." *Id.* at 1006 (citing *Eisai* 533 F.3d at 1357). Consistent with KSR, the court stressed that "[t]he requisite motivation can come from any number of sources and need not necessarily be explicit in the art." *Id.* Specifically, with regard to the first step, i.e., identification of a lead compound, the court found that Teva had "raised a substantial argument that compound 12 was a natural choice for further development…." *Id.* at 1007. The court identified several factors that led to this holding including: the prior art patent claimed that its compounds, including compound 12, were improved proton pump inhibitors compared to the prior art compounds; compound 12 was one of the more potent compounds disclosed in the prior art patent; expert testimony; and Altana's own selection of compound 12 for further development, even though pantaprazole was ultimately developed by other means. *Id.* at 1007-1009. The Federal Circuit in consideration of the recent admonition by KSR against using a rigid test rejected the notion that identification of a single lead compound is required, and

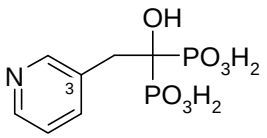
instead adopted the flexible approach that was used by the district court to conclude that one of skill in the art "would have used the more potent compounds of the '518 patent, including compound 12, as a starting point from which to pursue further development efforts." Id. 1008-9.

With regard to the next step modification of the lead compound, the Federal Circuit affirmed the district court's finding that Teva raised a substantial question that the combination of prior art references was "at the very least obvious to try and that such would lead to a predictable variation of compound 12, i.e., a compound with better pH [sic] stability." Specifically, the court found that the prior art taught that better stability for a compound in this class of drugs could be achieved with a lower pKa, and that this could be achieved by replacing a methyl with a methoxy. *Id.* at 1009. The court held that Altana failed to meet the burden of proof for granting a preliminary injunction. Judge Newman in her concurrence nonetheless found that the "evidence presented to the district court does not, in [her] view, establish invalidity of the patent on the pharmaceutical product pantoprazole." *Id.* at 1011.

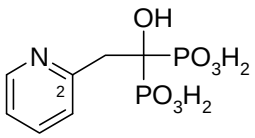
*Procter & Gamble*

In the fourth decision by the Federal Circuit, the patent at issue was directed toward the compound risedronate, the active ingredient in the osteoporosis drug Actonel®. *The Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009). Teva identified as its lead compound 2-pyr EHDP, a structural (or positional) isomer of risedronate. In risedronate (3-pyr EHDP), the hydroxy-ethane-diphosphonate group is connected at the third position of a pyridine ring, whereas it is connected to the second position of a pyridine ring in 2-pyr EHDP.

Risedronate




2-pyr EHDP




The Federal Circuit panel consisting of Circuit Judges Mayer and Dyk, and District Judge Huff, who wrote the opinion, in its obviousness analysis reasserted that the first step in an obviousness analysis based on structural similarity between claimed and prior art compounds is the "preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound. *Id.* at 994 (citing *Takeda* and *Eisai*). The district court found

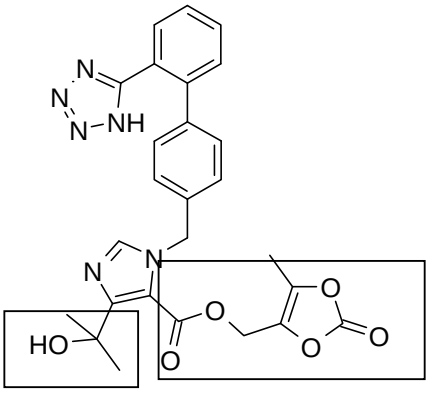
that the skilled artisan would not have identified 2-pyr EHDP as the lead compound. Nevertheless, the Federal Circuit never addressed the appropriateness of 2-pyr EHDPas a lead compound. Instead, the court concluded that defendants failed to establish that it would have been obvious at the time of the invention to modify 2-pyr EHDP to create risedronate. *Id.* at 995.

Addressing the second step in the lead compound analysis, i.e., motivation to modify the lead compound, the court found based on the prior art and expert testimony that the structural modification from a 2-pyr EHDP to a 3-pyr EHDP was not routine. Further, the court found that the nature of the class of compounds to which risedronate belongs, i.e., bisphosphonates, was extremely unpredictable at the time of the invention. *Id.* at 996-997. Accordingly, modification of the claimed compound would not have been obvious to try at the time of the invention. Thus, the court affirmed the lower court's ruling that the patent was not invalid.

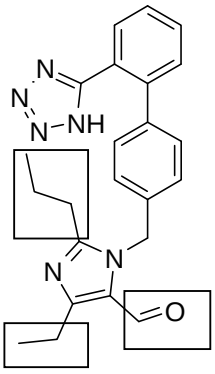
*Daiichi Sankyo*

The district court after a bench trial upheld the validity of a claim to a prodrug compound known as olmesartan medoximil, an ester, which is the active ingredient in several drugs that are angiotensin II receptor blockers (ARBs) used to treat hypertension, including Benicar and combinations Benicar HCT and Azor. *Daiichi Sankyo Company, Ltd., v. Mylan Pharmaceuticals Inc.,* 2009 WL 2356879 (D.N.J.). Mylan identified several compounds as potential lead compounds from a prior art '902 patent to Dupont. Mylan suggested these compounds were a continuation of Dupont's earlier research efforts that produced the first generation of ARBs, specifically losartan. In particular, one of the compounds is Example 1, which is shown below in comparison to olmesartan medoximil.

Olmesartan medoxomil




Example 1 of the '902 Patent



The district court rejected these compounds as leads based on Mylan's failure to prove why a person skilled in the art would have selected them over numerous other second generation ARBs in the prior art that relied on the same chemical backbone and had comparable, if not greater, improvements from losartan. *Id.* at 12-13. The court stated "[s]ince a person of ordinary skill in the art could have selected a lead compound from a 'broad selection of compounds,' Mylan has failed to establish its prima facie case of obviousness." *Id.* at 13.

Despite its finding that Mylan failed the first step for proving obviousness of a compound, *i.e,* identification of a lead compound, the court continued its analysis and found that one of skill in the art would not have been motivated to modify the '902 prior art compounds to form the claimed compound. Specifically, olmesartan medoxomil differed structurally in several respects to the compounds of the '902 patent at the 4- and 5- position of the imidazole ring. For example, the '902 patent taught various alkyls at the 4 position, including an ethyl, methyl, t-butyl, and isopropyl, while olmesartan medoximil has a hydroxyisopropyl group, which provides hydrophilic instead of lipophilic properties. The '902 patent also taught a carboxylic acid (Examples 2 and 6) or aldehyde (Examples 1, 3, 4 and 5) at the 5 position, while olmesartan medoximil possesses a carboxlic acid linked to a medoxomil acid.

The court found the prior art taught away from modifying the 4 position, and further, that it would have been illogical for one skilled in the art to undo the 4-position of the prior art compounds because it was this position and its substituents that gave the prior art compounds their advantageous lipophilic properties. *Id.* at 14-15. Regarding position 5, the court found that Mylan failed to show that one skilled in the art would have been motivated to transform the '902 compounds into a prodrug comprising medoxomil as a result of the unpredictable and difficult nature involved with prodrug pharmacology and reproducibility as well as the lack of motivation to select medoxomil. *Id.* at 16. Accordingly, the court found the claimed compound not invalid for obviousness.

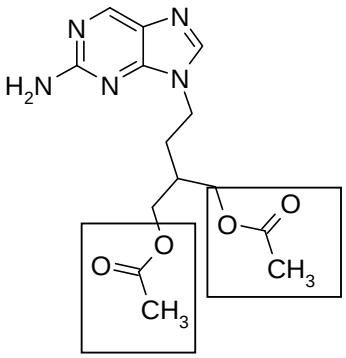
*Novartis*

Finally, the patent-at-issue was directed to famciclovir, Novartis' antiviral treatment for herpes. *Novartis v. Teva*, No. 05-1887 (D.N.J. 2007). The court denied Novartis' motion for a preliminary injunction to restrain Teva from releasing their generic famciclovir product. The court held that Novartis had failed to show that Teva's obviousness and inequitable conduct defenses lacked merit.

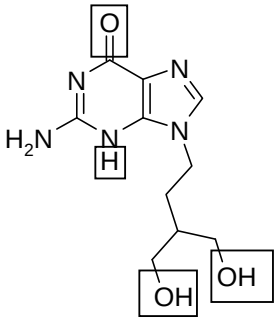
Famicolovir is a prodrug that is converted into an active compound inside the body. The active compound in famciclovir is penciclovir, an acyclic

nucleoside. Since the late 1970s, acyclic nucleosides have been recognized as potential anti-mitotic or anti-viral agents.

Famciclovir



Penciclovir



The court held that it was arguable that it would have been obvious to select penciclovir as a lead compound from which to design famciclovir because it was "one of only five known acyclic nucleosides to have strong activity and low toxicity". While *Takeda* held that when there are many potential lead compounds, the selection of one particular compound may not be an obvious choice, the court distinguished the present case on the basis that the prior art in *Takeda* disclosed "hundreds of millions" of potential lead compounds. Even though one article taught away from penciclovir, several other patents and applications taught that penciclovir was a potent antiviral agent. Thus, the court concluded that "prior art as a whole" did not "teach away" from using penciclovir as a lead compound.

The court also found that Novartis failed to make a persuasive argument to rebut Teva's allegations that it was obvious to modify penciclovir to create famciclovir. The court opined that a person of ordinary skill in the art would have expected penciclovir to share the poor oral bioavailability of other acyclic nucleosides. Teva highlighted British patent application No. GB 2130204, which instructs how to improve the bioavailability of compounds similar to penciclovir. While Novartis argued that it was "unknown" whether the modifications made to acyclovirs as described in the British application would have a similar effect on penciclovir, Teva countered that the obviousness inquiry does not ask whether a result is "unknown" but rather whether there is a reasonable probability of success. The court rejected Novartis' argument, which was the development of famciclovir was not obvious because it had unexpected advantages over penciclovir, for a number of reasons: (1) based on the prior art, such results had previously been produced; (2) Novartis' studies regarding

"dosing advantage" were not persuasive because it did not do a head-to-head comparison of the various treatments; (3) there was no evidence supporting a latency advantage for famciclovir over other drugs; and (4) these advantages were not related to the invention because they were not benefits achieved through modifications made to obtain famciclovir, but instead flowed from the inherent properties of penciclovir. Accordingly, the court denied the preliminary injunction.

The above cases strongly suggest that the lead compound framework for analyzing claims still applies to compounds *per se* despite *KSR* and that compound claims upon such analysis continue to be upheld by courts after being fully litigated.