

Legal Affairs

Redefining Obviousness After *KSR* Decision

Eisai Provides Some Greatly Needed Predictability for Biotech and Pharma

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One of the most difficult issues facing a patent system is determining how much of an advance over prior art is required for patentability. The inquiry of whether an invention is obvious in the U.S., and the similar inventive step test in Europe, involves challenging policy considerations into what type of work deserves a patent.

Because many important inventions seem obvious in hindsight, the framing of the obviousness inquiry often determines the answer that follows. For this reason inventors and patent attorneys eagerly anticipated the U.S. Supreme Court's *KSR* decision last year, its first major decision regarding the standard for obviousness in over 40 years.

When the Supreme Court issued the *KSR* decision, it did more to clarify what the test was not than what it actually was. The Biotechnology Industry Organization (BIO; www.bio.org) and the Pharmaceutical Research and Manufacturers Alliance (PhRMA; www.phrma.org) argued that the existing test developed by the Court of Appeals for the Federal Cir-

cuit, which required that the prior art show a "teaching, suggestion, or motivation" (TSM) before an invention is considered obvious, should be affirmed.

The Supreme Court rejected the TSM test. It found this approach too rigid, and, as a result, too many questionable patents issued. Part of the reason for the number of questionable patents was an overly rigid application of the TSM test without the application of common sense.

Since the *KSR* decision, both the Patent Office and courts have used common sense to find inventions relating to biotechnology and pharmaceuticals obvious. In particular, patents claiming innovations such as a nucleic acid encoding a novel cell-surface antigen, or an improved formulation for a contraceptive were found obvious using a common sense analysis. Thus, it appeared the fears of BIO and PhRMA of a weakened patent system were justified.

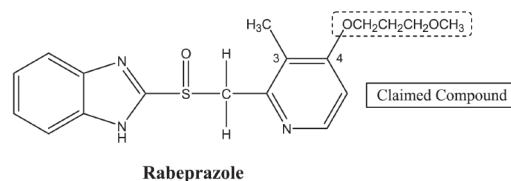
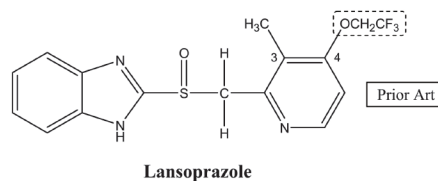
Validity of a Patent

A recent decision relating to two generic drug companies' challenges to the validity of an *Eisai* (www.eisai.com) patent

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covering Aciphex® (rabeprazole) may have restored sanity to the obviousness analysis and allayed some fears. *Eisai* claimed a novel pyridine derivative that was more potent than prior art compounds at inhibiting gastric acid secretion.

Prevacid® (lansoprazole), a prior art compound, used to treat or prevent ulcers, was a structurally similar pyridine derivative.



These two compounds differ only in the substituent on the pyridine ring: rabeprazole has a methoxypropoxy group (OCH₂CH₂CH₂OCH₃), while lansoprazole has a trifluoroethoxy group (OCH₂CF₃).

In reviewing the judgment of nonobviousness from the district courts, the Court of Appeals noted that the *KSR* decision required the identification of a starting reference point from which one of ordinary skill in the art could identify a problem and pursue potential solutions. Next, *KSR* required some reason to make modifications to the prior art to achieve the claimed compound.

Finally and crucially, in *Eisai*, under an obvious-to-try analysis there had to be some reason for narrowing the prior art universe to a “finite number of identified, predictable solutions.” In other words, one of ordinary skill should have a basis for choosing the prior art compound to be the lead compound.

Here, the obvious structural and functional similarities between the two compounds suggested that lansoprazole could be a lead compound. Both lansoprazole and rabeprazole are small, lipophilic molecules having a molecular mass of about 360 g/mole. These similarities, however, were insufficient alone to support a finding of obviousness.

The Court of Appeals looked further and found that the function of lansoprazole as an antiulcer treatment would not lead one of ordinary skill to use it as a lead compound to discover a gastric acid inhibitor. In particular, the data for lansoprazole did not suggest that it inhibited gastric acid secretion. The function of lansoprazole does not, however, resolve the question of

whether it would have been a desirable lead compound, and so the Court of Appeals looked to whether there were any contrary indications to lansoprazole as a lead compound.

As it turned out, the structural difference between lansoprazole and rabeprazole represented a contrary indication, a “teaching away”, to modifying lansoprazole to obtain rabeprazole even if lansoprazole had been selected as a lead compound. The evidence indicated that the fluorinated substituent of lansoprazole increased lipophilicity. One of skill in the art would have understood that increased lipophilicity was a desired characteristic in an antiulcer treatment.

There was no reason why one of ordinary skill would choose lansoprazole as a starting material and remove an advantageous feature of that compound. By moving in a direction contrary to conventional wisdom, Eisai discovered an unexpectedly superior proton pump inhibitor. Accordingly, the Court of Appeals affirmed the finding of nonobviousness.

Identify the Lead Compound

Eisai’s focus, on “the reasoned identification of a lead compound” as a starting point for obviousness analysis after *KSR*, seems logical in terms of looking at drug development from an investment perspective. In the last 10–15 years, techniques such as high-throughput screening of small molecules and nucleic acid microarrays have greatly increased the ability to identify promising compounds.

These compounds then undergo costly preclinical testing to assess their potential as a therapeutic. An even smaller number of compounds show sufficient promise to enter clinical testing.

At this stage, it is estimated that only one in ten drugs that enter clinical testing receives FDA support. Given this costly drug discovery and development process, one would not want to randomly modify compounds for development. Thus, requiring “the reasoned identification of a lead compound” is a fair method to determine what novel chemical compounds are obvious.

Stronger Patent Systems

As BIO and PhRMA argued in the *KSR* decision, a strong patent system is necessary to support the investment needed to fund costly research and development. A predictable test for obviousness that avoids the trap of hindsight analysis is an important step in strengthening confidence in use of patents to protect investment in research and development. The *Eisai* decision provides greatly needed predictability for the biotechnology and pharmaceutical industries by (1) restating that the proper starting point for an obviousness analysis for a chemical compound is the reasoned identification of a lead compound, and (2) affirming the importance of secondary considerations of nonobviousness such as teaching away and unexpected results. **GEN**