Since KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007), the Court of Appeals for the Federal Circuit has rendered several decisions in which the obviousness of a chemical compound was at issue. Patents for chemical compounds are at the core of patent protection for small-molecule drugs and therefore the impact of KSR on obviousness is important to the pharmaceutical industry at all levels—from start-ups to “big pharma.” Prior to KSR, there was established case law addressing several obviousness scenarios unique to chemical practice. The Federal Circuit does not see the KSR decision as upending the established case law at issue in these particular disputes.

In Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350 (Fed. Cir. 2007), Alphapharm, a generic drug manufacturer, had filed an Abbreviated New Drug Application to make a generic version of one of Takeda’s compounds, pioglitazone. As part of its defense against Takeda’s infringement claims, Alphapharm argued that Takeda’s patent on pioglitazone was invalid because a prior art compound, which differed only slightly from pioglitazone (identified as “compound b”), rendered pioglitazone obvious. Both compounds include a ring of five carbons and one nitrogen, a pyridyl ring. Compound b has a methyl group (a group containing only one carbon) at position 6 on the pyridyl ring. Pioglitazone has an ethyl group (containing two carbons) at position 5 on its pyridyl ring (one carbon over from position 6). Alphapharm contended that these changes were structurally obvious because they were examples of two practices common in the pharmaceutical industry: replacing one group with a similar group (methyl to ethyl) or homologization, and “ring-walking” the substituent group from position 6 to position 5 on the pyridyl ring. The district court, ruling before KSR, found that compound b was not an obvious choice to modify to make an antidiabetic because one of its side effects is weight gain. Weight gain, while generally undesirable, is even less so in diabetic patients. Additionally, compound b is toxic and therefore less suitable for treatment of chronic diseases, like diabetes. On appeal to the Federal Circuit, Alphapharm argued that the changes to get from compound b to pioglitazone were “obvious to try,” citing the intervening KSR opinion. The appellate court, however, affirmed the lower court and upheld the validity of the Takeda patent. As part of its decision, the court pointed to the unexpected properties of pioglitazone. The toxicity and other side effects of compound b, the closest prior art, taught away from the claimed invention and so the prior art did not suggest modifying compound b either by homologization or ring-walking. Additionally, the possible alternatives to the original methyl in the 6 position were enormous. The court stated that therefore this was not the “obvious to try” situation contemplated by the Supreme Court in KSR because compound b’s negative properties and the numerous substitutions from which to choose when replacing the original methyl group in the 6 position.

In In re Sullivan, 498 F.3d 1345 (Fed. Cir. 2007), the applicants for a patent claimed invention of a compound using portions of an antibody called “Fab fragments” to neutralize snake venom. During prosecution, the examiner had rejected the claims as obvious over references to using the entire antibody to neutralize snake venom and a reference that discloses a method of making the Fab fragments, using the Fab fragments to detect snake venom. Additionally disclosed in a prior art reference was that for the purpose of detecting snake venom, Fab fragments had similar results to whole antibodies. Additionally, the U.S. Patent and Trademark Office argued that this application was merely a new use for a known composition. The applicants had submitted declarations showing that there was evidence to suggest that Fab fragments would not work as well as whole antibodies for neutralizing snake venom and therefore, the fact that Fab fragments do indeed work to neutralize snake venom was an unexpected result. The Federal Circuit sided with the applicants, citing back to In re Papesch, 315 F.2d 381 (CCPA 1963) for the proposition that a compound and all of its properties are inseparable and so the unexpected property of the Fab fragments led to a use that was not just new but also unexpected.

In Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293 (Fed. Cir. 2007), the compound in question was the drug ramipril, which has several different isomers. Isomers are compounds that share the same chemical formula but have different structure and potentially dramatically different properties. The isomers of ramipril are stereoisomers, which means that their structures differ in the configuration in space of the atoms attached to a central atom. Stereoisomers are distinguished by using R and S designations for each point, or
stereocenter, in the molecule that leads to a stereoisomer. Ramipril has five such stereocenters.

Aventis had a patent on the form of ramipril where each stereocenter had the S conformation, known as 5S ramipril. Additionally, the claim included the limitation that it was substantially free of other isomers of ramipril. Ramipril generally is in the prior art. Therefore, the novelty of the Aventis claim was in 5S ramipril substantially free of the other isomers.

Aventis sued Lupin for patent infringement after Lupin, a generic manufacturer, filed an Abbreviated New Drug Application for a generic version of ramipril. Seeking to invalidate the Aventis patent, Lupin argued that it was obvious to separate a mixture of ramipril isomers to get purified 5S ramipril. The district court, ruling prior to the KSR decision, decided in favor of Aventis, finding that there was no teaching, suggestion or motivation to separate the isomers in a mixture to produce pure 5S ramipril. The Federal Circuit, ruling after KSR, found that the district court had applied the teaching, suggestion or motivation doctrine too rigidly, as KSR warned against doing. Citing KSR, the Federal Circuit explained that it was only necessary to show “some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” The court then cited a 1978 U.S. Court of Customs and Patent Appeals (CCPA) ruling for the proposition that if it is known that a desirable property of a mixture is due to one of the components of that mixture, then purifying that one component is obvious even if there is no explicit teaching to separate the mixture and purify that one component. The court also cited to CCPA decisions from 1960 and 1938 in which purified components from known mixtures were held to be obvious. While the Federal Circuit found that the district court had erred in its application of the teaching, suggestion or motivation doctrine, the court additionally cited to pre-KSR decisions in support of its reversal of the district court.

More recently, in Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc. 520 F.3d 1358 (Fed. Cir. 2008), the Federal Circuit affirmed the validity of Ortho McNeil’s patent on the epilepsy drug, topiramate. Mylan Laboratories had filed an Abbreviated New Drug Application to market a generic version of topiramate and Ortho McNeil sued for patent infringement in response. As part of its defense, Mylan argued that the Ortho patent was invalid due to obviousness. Topiramate was invented as part of a research program to develop drugs that are FBPase inhibitors for treatment of diabetes. Topiramate was an intermediate compound made in the synthesis of an FBPase inhibitor. Mylan, relying on KSR, argued that it was obvious to try to build drugs that are FBPase inhibitors for the treatment of diabetes. The court however found that Mylan’s expert was viewing the research pathway with hindsight and that it would not have been obvious at the time of the invention because there were so many different possible starting compounds and different pathways to produce the desired compound. While the court acknowledged KSR’s warning against rigid application of the teaching, suggestion or motivation doctrine, the court pointed to its own post-KSR decision stating that a TSM test, flexibly applied, is necessary to avoid hindsight analysis. In re Translogic Tech., Inc. 504 F.3d 1249 (Fed. Cir. 2007). The court also noted that in order for topiramate to be obvious, it would have had to have been obvious to stop at this intermediate compound in the synthesis and test it for anti-convulsive properties.

While KSR is casting a new hue on obviousness analysis also for chemical compounds, these early cases seem to indicate that pre-KSR caselaw continues to be relevant and applied by the Federal Circuit. Patent practitioners are likely to find that while new compounds claims are more likely to withstand obviousness challenge, optimization claims to different salt forms, excipients, dosages, and the like are likely to be rejected or invalidated for obviousness. However, the effect of KSR and subsequent Federal Circuit cases to claims to new administration forms or new combinations is harder to predict, and their validity is likely to depend on showing unexpected results, such as synergy or superior therapeutic efficacy.

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