VALIDITY OF PATENTS DIRECTED TO POLYMORPHS

A recent decision from the Federal Circuit, *Grunenthal GMBH v. Alkem Laboratories Limited*, Appeal No. 2017-1153 (Fed. Cir. March 28, 2019) has made it more difficult to challenge the validity of claims directed to polymorphs and use thereof. A polymorph is a chemical compound that can be present in more than one three-dimensional crystalline structure. An issue before the Court was whether a disclosure of a polymorph of a compound in the prior art and a known approach for polymorph screening renders obvious under 35 U.S.C. §103 an unknown polymorph of the same compound having the same utility as the known polymorph.

U.S. Patent No. 7,994,364 ("'364 patent), assigned to Grunenthal GMBH ("Grunenthal"), claimed a polymorph form of tapentadol hydrochloride, identified as Form A and a method of treating pain and/or urinary incontinence using Form A polymorph. The defendants argued that the claims were unpatentable as being obvious under 35 U.S.C. §103 in view of the teachings of U.S. Patent No. 6,248,737 ("'737 patent), assigned to Grunenthal, which discloses a different polymorph form of tapentadol hydrochloride, known as Form B and a 1995 article by Byrn et al. ("Bryn") which discloses a conceptual general approach to the characterization of pharmaceutical solids, including a flow chart of investigative steps to determine whether polymorphs are possible. The Bryn article suggested different variables that may be adjusted during recrystallization to determine whether polymorphism occurs in a compound. Further, the Bryn article lists a number of solvents to be used for recrystallization of a solid to first determine whether polymorphs are possible. According to the article, solvents "should include those used in the final recrystallization steps and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone acetonitrile, ethyl acetate, hexane and mixtures, if appropriate". The Bryn article instructs a person of ordinary skill in the art to vary other variables, such as temperature, concentration, agitation and pH, during the recrystallization process. However, the Bryn article does not provide guidelines regarding which temperature, concentration, agitation, or pH levels would likely result in polymorphs of particular compounds. The Bryn article just provides generalities and is not enabling for the preparation or identification of any specific polymorph.

Obviousness is a question of law, with underlying factual findings related to, *inter alia*, (a) the scope and content of the prior art, (b) whether a person of ordinary skill in the art ("POSA") would have reason to combine or modify the prior art to arrive at the claimed invention and (c) in so doing, would have a reasonable expectation of success. The Court focused on the reasonable expectation of success. The Court held that the claimed invention was non-obvious over the cited art. In particular, the Court focused on the fact that polymorph A was unknown at the time of the filing of the underlying application of the'364 patent. The record indicates that only about 30-35% of all compounds are polymorphic, so that the existence of polymorph A was reasonably unpredictable at the time of filing of the underlying application of the '364 patent. In addition, the Court reasoned that the Bryn article merely identified the variables to be considered; but, the Bryn article does not provide sufficient guidance "in discussing the wide array of conditions that would affect recrystallization and therefore the crystal structure of the resulting compound." In other words, according to the Court, the Bryn article was too general in nature and not enabling to make a particular polymorph. The Bryn article provided insufficient guidance in discussing the wide array of conditions that could affect recrystallization, and therefore, the crystal structure of a resulting compound.

The defendants argued that any polymorph screening of tapentadol hydrochloride would result in Form A because Form A is more stable at room temperature than Form B, and thus one of ordinary skill in the art would expect that Form A would be formed in preparing any polymorph of tapentadol hydrochloride. They referred to Example 25 of the '737 patent, which discloses three specific steps for synthesizing tapentadol hydrochloride. Although the defendants tried to argue inherent anticipation and although its experts produced a sample of tapentadol hydrochloride that comprised a mixture of Form A and Form B, the Court found that the defendants had not performed all of the steps of Example 25, but only one of the steps. On the other hand, testimony of the plaintiff showed that performing all of the three steps outlined in Example 25 resulted in only Form B.

The Court reasoned:

> Because the record indicates that there was (1) no known or expected polymorphism of tapentadol; (2) no evidence that the synthesis of Example 25 results in any Form A; and (3) no guidance as to what particular solvents, temperatures, agitation rates, etc., were likely to result in Form A, Alkem failed to prove that a POSA would have reasonably expected a polymorph screening of the Form B disclosed in the '737 patent to result in Form A.
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> … Here, a POSA did not know, or have reason to know, that tapentadol hydrochloride is polymorphic. Nor could a POSA know, or have reason to know, how the multiple variables involved in conducting a polymorph screen would affect the recrystallization of tapentadol hydrochloride. Byrn does not provide any guidance as to how the different solvents, varying temperatures, rates of agitation, or other variables used in polymorph screenings should be manipulated to even determine whether polymorphism occurs…This lack of knowledge in the field shows there was little to no basis from which a POSA could expect a probability of success in producing Form A.
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> The defendants also argued that because the Bryn article discloses a finite number of solvents to use for recrystallization, it would have been obvious to try to produce Form A of tapentadol hydrochloride. To prove obviousness under an obvious to try theory, the defendant had to show "(1) a design or market need to solve a particular problem, and (2) that 'there are a finite number of identified, predictable solutions' that would lead to an expectation of success".
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> Focusing again on the reasonable expectation of success prong, the Court reasoned:
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> Rather, Byrn simply provides "a general approach" to polymorph screening, only giving "general guidance," without providing "detailed enabling methodology." …This court has explained that a conclusion of obviousness does not follow from merely "vary[ing] all parameters or try[ing] each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful."…

The Court held that the claims of the '364 patent were valid over the prior art.

Although the Court indicated that the decision "does not rule out the possibility that polymorph patents could be found obvious," it is my opinion that this decision reinforces the difficulty in invalidating a polymorph patent. According to the record, only 30-35% of all compounds are polymorphic. As long as there is no prior art reference that teaches the existence of a particular polymorph of a given compound and/or as long as there is no prior art references that provide an enabling disclosure for making the particular polymorph of a given compound, this decision by the Federal Circuit suggests that a patent directed to a particular polymorph would be held valid, if challenged, as there is no reasonable expectation of success that it could be proven that the particular polymorph existed at the time of the filing of the underlying application of the polymorph patent. General screening tests for predicting polymorphism is insufficient to invalidate a patent for polymorphs. Moreover, to prove that a prior art reference discloses a particular polymorph, the procedure described in the prior art reference must be followed exactly; any deviation from the procedure in the prior art, according to *Grunenthal*, weakens any argument for invalidity.