CAFC Upholds Validity of Formulation Claim (Fortical®)

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On August 25, 2011, the Court of Appeals for the Federal Circuit (CAFC) upheld a District Court's grant of summary judgment of non-obviousness with respect to a pharmaceutical composition comprising salmon calcitonin and a specific concentration of citric acid and other components. The case is *Unigene Labs v. Apotex*.

The case focused on the following claim from U.S. Reissue Patent No. RE40,812E (the '812E patent):

> 19. A liquid pharmaceutical composition for nasal administration comprising about 2,200 MRC units of salmon calcitonin, about 20 mM citric acid, about 0.2% phenylethyl alcohol, about 0.5% benzyl alcohol, and about 0.1% polyoxyethylene(2) sorbitan monooleate.

Salmon calcitonin is a known regulator of calcium in the blood and therefore useful for the treatment of osteoporosis. The claimed formulation allows the delivery of the calcitonin peptide through a nasal spray, which is an effective method for overcoming the drug's poor bioavailabilty. When filing a New Drug Application for this formulation (Fortical®), Unigene demonstrated bioequivalence with Miacalcin®, another nasal formulation comprising salmon calcitonin. The Fortical® and Miacalcin® formulations use different components to act as both an absorption enhancer and a surfactant: Fortical® relies on 20 mM citric acid for this function, while Miacalcin® uses benzalkonium chloride (BZK).

Referring to the Miacalcin® formulation as the "reference composition," the court held that one of skill in the art would have had no motivation to replace BZK with 20 mM citric acid. In its review of certain secondary references, the court noted that one U.S. patent disclosed solid, not liquid, oral dosage forms, as well as concentrations of citric acid that were much higher than what was claimed. The court also noted that another publication disclosed the use of citric acid in liquid nasal sprays, but as a "pH adjuster or buffer," not a surfactant or preservative.

Finally, the court cited another U.S. patent's teaching that citric acid was an acidic component of the buffer, and not an absorption enhancing agent. The court also proposed that this patent taught away from the use of citric acid, as it referenced another study in which citric acid yielded "discouraging" test results.

In view of this analysis, the court took the position that even if "there was a design need and market pressure to develop a pharmaceutical formulation that is bioequivalent to Miacalcin®, there is no evidence in the record that claim 19 would be an obvious solution to those motivations." In fact, the court held that "the 'about 20.0 mM citric acid' limitation alone supports the district court's grant of summary judgment of nonobviousness."

Of interest in the *Unigene* case are the parallels that the court drew between the "lead compound" obviousness analysis used for a novel chemical entity and that used for a pharmaceutical formulation. The lead compound analysis is based on the identification of a "lead" prior art compound, as well as some direction in the art to structurally modify that lead (see, *e.g.*, *Daiichi Sankyo v. Matrix Laboratories* (CAFC, 2010)). Because the structure of a compound is not always as important as its pharmacokinetic properties in a pharmaceutical composition, the court noted that "reference composition" would be more suitable a phrase than "lead compound" when asking questions of obviousness for a pharmaceutical formulation.

Outside of determining that Fortical® was not obvious in view of Miacalcin®, the court did not further expand on the applicability of the proposed "lead "reference composition" test. It is possible that such an analysis will be narrowly applied to cases in which bioequivalence was established between new and previously known formulations: "[i]n the context of a…formulation patent where the patented formulation was made to mimic a previously FDA-approved formulation…the term 'reference composition' is more appropriate… when considering obviousness for a chemical [formulation] that the infringer deliberately imitates."

One could speculate, though, that the court has lay the groundwork for a more broadly applicable pharmaceutical formulation analysis formally requiring the identification of a "lead" formulation that one of skill in the art would want to modify, as well as a *reason* in the art to modify the formulation in a particular way. Indeed, such an analysis has been informally used, for example, in *Abbott v. Sandoz* (CAFC, 2008), in which the court held that one of skill in the art would not be motivated to replace the Azithromycin component of a prior art formulation with Clarithromycin, due to the different pharmacokinetic properties of these drugs, as well as the high number of possible formulation options.

Future cases in this area will confirm whether the court is slowly developing a guiding (but not strict) rule for determining the obviousness of a new pharmaceutical formulation.

If you have any questions about this case, or any other aspect of chemical/pharmaceutical patent law, please contact your Lathrop Gage attorney or one of the attorneys listed on this alert.