WSGR ALERT

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UNIGENE V. APOTEX: FEDERAL CIRCUIT DISCUSSES STANDARD FOR PRIMA FACIE OBVIOUSNESS OF PHARMACEUTICAL COMPOSITION CLAIMS POST-*KSR*

On August 25, 2011, the United States Court of Appeals for the Federal Circuit issued a decision in *Unigene v. Apotex*, No. 2010-1006,[1] affirming the lower court's summary judgment of non-obviousness and addressing what is necessary post-*KSR* to establish a prima facie case of obviousness for pharmaceutical formulation patents claims. This decision is significant because the Federal Circuit applied a modified form of the structural obviousness analysis typically used for a chemical compound claim to a pharmaceutical formulation claim in a manner that has the potential to make it more difficult to invalidate pharmaceutical formulation claims for obviousness—particularly those that are more narrowly directed to a specific combination of an active drug and/or excipient(s), which are often referred to as "picture" or "fingerprint" claims.

Background

Plaintiff Unigene manufactures Fortical, a nasal spray calcitonin formulation meant to treat post-menopausal osteoporosis. Fortical is an alternative formulation of another calcitonin-based drug, Miacalcin, sold by Novartis. Unigene filed its New Drug Application (NDA) for Fortical under 21 U.S.C. § 505(b)(2), naming Novartis's Miacalcin as the reference listed drug. Unigene also filed a patent application on its formulation, which issued as U.S. Patent No. 6,440,392 and was reissued as RE40,812E. Unigene asserted the '812E patent against Apotex in the District Court for the Southern District of New York in response to Apotex filing an Abbreviated New Drug Application (ANDA) containing a Paragraph IV certification that indicated an intent to make, use, offer to sell, sell, and/or import a generic version of Unigene's Fortical product. Only claim 19 was asserted, which reads as:

> "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."

The district court granted Unigene's motion for summary judgment that claim 19 was not obvious as a matter of law, finding that "no prior art teaches using 20 mM citric acid to achieve 'both shelf stability and enhanced bioavailability' in a nasal salmon calcitonin formulation . . . [and] that it would not have been obvious to a person of ordinary skill in the art to modify Miacalcin to reach the formulation of claim 19."[2] The Federal Circuit, in affirming the lower court's ruling, selected Miacalcin as the reference pharmaceutical composition and then found the prior art insufficient to establish a prima facie case of obviousness.

Federal Circuit's Obviousness Analysis

The court in *Unigene* began its obviousness analysis by stating that "[o]bviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention."[3] Furthermore, the court stated, "[W]hen design need and market pressure may dictate a commonsensical path using a finite number of identified predictable solutions to one of ordinary skill, deviations from that path are likely products of innovation."[4] The Federal Circuit then discussed two rules for establishing obviousness that were previously outlined in *Bayer Schering v. Barr*, both of which the court applied in *Unigene*.[5] First, "[t]o render a claim obvious, prior art cannot be 'vague' and must collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution."[6] Second, "[w]hen a field is 'unreduced by direction of the prior art,' and when prior art gives 'no indication of which parameters were critical or no direction

[1] *Unigene, Labs., Inc. v. Apotex, Inc.*, No. 2010-1006, 2011 WL 3715557 (Fed. Cir. Aug. 25, 2011).
[2] *Id.* at *4.
[3] *Id.* at *6 (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418, 421 (2007)).
[4] *Id.* at *7.
[5] *Id.* (citing *Bayer Schering Pharm. AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009)).
[6] *Id.* at *7, *9 (citations omitted) (emphasis added).

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as to which of many possible choices is likely to be successful,' an invention is not obvious to try."[7]

The Federal Circuit found that there was a "design need" and "market demand" to "create an FDA-approved liquid nasal composition that delivers salmon calcitonin," but that there was "no evidence in the record that claim 19 would be an obvious solution to those motivations."[8]

The Function of the Components in Prior Art Formulations

The court stated that "[a]lthough [the asserted] claim does not assign any particular functionality or property to its list of components," the primary issue in the obviousness analysis of *Unigene* was whether the citric acid in the Fortical formulation would "be an obvious substitute for BZK's functions as an absorption enhancer and as a surfactant" in the Miacalcin formulation.[9] In discussing how to establish a prima facie case of obviousness for pharmaceutical formulation claims, the court noted that while "a lead compound is often used to show structural similarities between the claimed compound and prior art" for a chemical compound claim, "[i]n the context of a composition or formulation patent where the patented formulation was made to mimic a previously FDA-approved formulation, the functional and pharmaceutical properties of the 'lead compound' can be more relevant than the actual chemical structure"; therefore, "the term 'reference composition' is more appropriate than 'lead compound' when considering obviousness for a chemical composition that the infringer deliberately imitates."[10] Thus, the Federal Circuit applied the "lead compound" aspect of the obviousness analysis for chemical compound claims but focused on the "functional and pharmaceutical properties" of the lead composition and the claimed components in its obviousness analysis of chemical formulation claims.

The court emphasized that the lead composition "Miacalcin® contains . . . benzalkonium chloride ('BZK') which functions as a preservative, absorption enhancer, and surfactant. In contrast, Fortical® contains 20 mM of citric acid, which functions as an absorption enhancer and stabilizer/buffer; polyoxyethylene(2) sorbitan monooleate ('polysorbate 80'), which acts as a surfactant; and phenylethyl alcohol and benzyl alcohol, which serve as preservatives."[11] The Federal Circuit found "that the inclusion of 'about 20 mM citric acid' in the composition provide[d] the strongest case for non-obviousness."[12]

In reaching its decision, the court distinguished the prior art by describing how the art would not "give a person of ordinary skill sufficient reason or motivation to use" citric acid as a functional substitute for BZK in a liquid nasal salmon calcitonin composition.[13] The court distinguished the prior art '014 patent, despite its discussion of increasing bioavailability of salmon calcitonin by using citric acid, by explaining how its formulation was orally and not nasally ingested, and that this formulation was to be used on rats, not humans.[14] The court added that the prior art '315 patent "teaches away from using . . . citric acid as an absorption enhancing agent or stabilizing agent" because it discusses another patent that lists over 50 examples, including citric acid, of potential absorption agents but that all these examples yielded "discouraging" results and that "only ammonium tartrate" served as a satisfactory stabilizing agent.[15] Lastly, the Day reference, a general publication about pharmaceutical preformulation and formulation, apparently listed benzyl alcohol, phenylethyl alcohol, and BZK as three of nine listed preservatives and polysorbate 20 and 80 as one of three surfactants used as excipients in aqueous nasal products. The court nevertheless distinguished this reference because "[c]itric acid is not included in the list of preservatives, but appears instead as a pH adjuster or buffer."[16] The court concluded its discussion of the prior art by emphasizing how citric acid in the prior art was not described as a chemical that could perform the functions of citric acid in Fortical, and that when citric acid was described as having such functions in the prior art, it was one out of a large number of options that did not work satisfactorily.[17]

Obviousness Analysis from *Pfizer* to *Unigene*

The outcome in *Unigene* stands in contrast to the Federal Circuit's decision in *Pfizer v. Apotex*, which was issued one month before the Supreme Court's *KSR* decision. *Pfizer*

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[7] *Id.* at *7, *10 (citations omitted).
[8] *Id.* at *8, *10.
[9] *Id.* at *8-9 (emphasis added).
[10] *Id.* at *8 (citations omitted) (emphasis added).
[11] *Id.* at *2.
[12] *Id.* at *9.
[13] *Id.*
[14] *Id.*
[15] *Id.* at *10.
[16] *Id.*
[17] "When used as an absorption enhancer in the '116 patent, citric acid was one of over fifty options. *See KSR*, 550 U.S. at 421. Further, when the prior art used citric acid at about 20 mM, as in the '315 patent, it was used only as a buffer. There is no genuine dispute of material fact that a person of ordinary skill attempting to make a liquid composition to deliver salmon calcitonin into a human body through nasal administration would not have considered using about 20 mM citric acid with the narrowly claimed amounts of benzyl alcohol, phenylethyl alcohol, and polysorbate 80, because the formulation would not be expected to perform properly to meet the specificity of a pharmaceutical use." *Id.* (emphasis added).

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reversed a district court judgment by deciding that a claim on a besylate salt formulation containing the known active compound amlodipine was obvious in light of the prior art, which disclosed a maleate salt formulation of amlodipine.[18] In reversing the lower court's finding of non-obviousness, the court in *Pfizer* engaged in an extensive discussion on the structural characteristics of the besylate salt formulation versus the maleate salt formulation and how the structural shortcomings of maleate would have led one skilled in the art to the besylate formulation—a discussion lacking in *Unigene*.[19] In contrast, the court in *Unigene* did not engage in a structural comparison of the Fortical and Miacalcin formulations as a basis for obviousness, and instead focused primarily on whether the prior art disclosed an identical function for one of the formulation components even though the claim at issue did "not assign any particular functionality or property to its list of components."[20]

For more information on this decision, or for further guidance on how to evaluate your intellectual property and litigation strategy in light of this decision and its potential implications, please contact a member of Wilson Sonsini Goodrich & Rosati's IP litigation, generics, or IP counseling and patents practices.

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[18] *See Pfizer v. Apotex*, 480 F.3d 1348 (Fed. Cir. 2007).
[19] *Id.* at 1361-2.
[20] *Unigene*, 2011 WL 3715557, at *8.

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