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Are Combination Drugs in Danger After the Federal Circuit's *Novo Nordisk* Decision?

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Legal Update

The Federal Circuit rendered a decision in *Novo Nordisk A/S v. Caraco Pharmaceutical Laboratories, Ltd.* on June 18, 2013, finding that a Novo Nordisk diabetes treatment patent involving the combination of the drugs metformin and repaglinide was an obvious combination of known diabetes treatment drugs, despite certain factual findings of the combination's unexpected results. Combination drugs, such as Novo Nordisk's metformin-repaglinide treatment for diabetes, have been increasingly found to be effective for treating a variety of ailments, but their development is typically incredibly expensive and time-consuming. This Federal Circuit decision could adversely affect investment in developing combination drugs, which in turn would affect the availability of these often very effective treatments. The decision also highlights the deference (or lack thereof) given to patent examiner findings during prosecution.

The case further involved an inequitable conduct dispute in which the Federal Circuit reversed the lower court's finding of inequitable conduct, but this dispute involves issues largely unrelated to the focus of this article.

Obviousness of Combination Drugs

With respect to the obviousness question before the Federal Circuit, the parties did not dispute that metformin and repaglinide were known as individual diabetes treatment drugs. Novo Nordisk and Caraco also did not dispute that combining drugs to treat disease was generally known at the time of the invention, or that it would have been obvious to try combining metformin and repaglinide. Instead, the obviousness inquiry focused on whether the particular combination of metformin and repaglinide achieved unexpected results, namely synergistic effects, so as to negate a finding of obviousness.

The Federal Circuit agreed with the district court's factual findings that: (1) the closest prior art was combination therapy using metformin and sulfonylurea, which is an insulin secretagogue; (2) the combination of metformin and the sulfonylurea class of insulin secretagogues was known at the time of the invention; and (3) repaglinide was known at the time of the invention as an insulin secretagogue. The court therefore concluded that the claimed metformin-repaglinide combination was obvious because it would have been reasonable for a person skilled in the art to use metformin with the known insulin secretagogue repaglinide, rather than the known insulin secretagogue sulfonylurea. In other words, the court concluded it would have been obvious to replace one known insulin secretagogue with another.

In reaching this conclusion, the lower court dismissed Novo Nordisk's arguments and evidence regarding the dissimilarity of sulfonylurea and repaglinide. In particular, Novo Nordisk argued that sulfonylurea and repaglinide are not chemically similar and hence are not obvious substitutes of one another. In other words, the synergy of metformin and some classes of insulin secretagogues, *e.g.*, sulfonylurea, does not reflect on the synergy of metformin and other classes of insulin secretagogues, *e.g.*, repaglinide. Novo Nordisk supplied evidence demonstrating these chemical dissimilarities, as well as the unexpectedly good synergism of metformin and repaglinide—results on the order of 800% improvement! On appeal, the Federal Circuit nevertheless held that these unexpected results were not sufficient to overcome the Federal Circuit's clear-error standard for review of district court factual findings.

The Federal Circuit's decision highlights the high deference afforded to district court findings of fact underlying the

determination of obviousness, even in view of evidence that demonstrates potential flaws in the district court's factual conclusion. Parties in district court litigation should be particularly vigilant in providing evidence and arguments in favor of non-obviousness because they will face a high hurdle on appeal.

This case also highlights the difficulty of establishing non-obviousness when claim elements are individually known. Since combination drugs are often combinations of known elements in different combinations than previously known, as opposed to combinations including a completely new element, the Federal Circuit raises grave concerns for combination drug patent holders and applicants since even evidence of 800% improvement failed to convince the courts of unexpected synergy. As stated in the dissent by Judge Newman, the majority's decision effectively punishes inventors who pursue combinations known to be unpromising and seems to suggest that only random combinations could ever be deemed as non-obvious. These concerns could adversely affect pharmaceutical researchers who spend extensive amounts of time and money to develop combination treatments.

Patent applicants may be able to address some of these concerns during patent drafting and prosecution when the opportunity exists to introduce ample evidence of unexpected results and/or to distinguish new combinations from other known or similar combinations. Such disclosure in the application itself, or in arguments presented to the United States Patent and Trademark Office (USPTO), will make it more difficult for a district court to overlook dissimilarities between known elements and the results achieved by the claimed combination.

Deference to USPTO Factual Findings

In challenging the obviousness determination, Novo Nordisk also argued that the court should defer to the USPTO finding, written on the record by the Examiner, that the combination of metformin and repaglinide achieved unexpected results and was therefore not obvious. These arguments were presented by Novo Nordisk with reference to the U.S. Supreme Court 2012 decision in *Kappos v. Hyatt* in which the Court addressed deference to USPTO findings in a court review of a USPTO rejection.

The Federal Circuit expressly declined to defer to the underlying USPTO findings made during prosecution, while distinguishing such deference from the presumption of validity of an issued patent. In particular, the Federal Circuit stated:

> The initial determinations by the PTO in determining to grant the application are entitled to no deference as they would be in an appeal to this court under 28 U.S.C. § 1295(4)(A) or (absent new evidence) in a district court proceeding under 35 U.S.C. § 145. Rather, we treat the issued patent as having a presumption of validity that must be overcome by clear and convincing evidence. No decision of the Supreme Court or this court has ever suggested that there is an added burden to overcome PTO findings in district court infringement proceedings, and we reject Novo's contrary assertion. Neither are we persuaded that the presence or absence of PTO findings on particular issues affects the basic presumption of validity.

These statements further highlight the importance of arguments made at the district court level that could affect the district court's findings even when a patent's prosecution record explicitly provides relevant evidence.

What's Next?

On August 16, 2013, Novo Nordisk petitioned the Federal Circuit for an *en banc* rehearing of its June 18, 2013 decision. This petition may be granted in view of the lengthy legal history of Novo Nordisk and Caraco's dispute, as well as the serious industry implications of the Federal Circuit's decision. In the meantime, practitioners should remain aware of the concerns raised by this case for combination drugs, and the issues surrounding "unexpected results" in general.

This advisory was prepared by Nutter's Intellectual Property practice. For more information, please

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