United States Court of Appeals for the Federal Circuit

NOVO NORDISK A/S AND NOVO NORDISK INC.,
Plaintiffs-Appellants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Appellees.

2011-1223

Appeal from the United States District Court for the Eastern District of Michigan in No. 05-CV-40188, Judge Avern Cohn.

Decided: June 18, 2013

MARK A. PERRY, Gibson, Dunn & Crutcher LLP, of Washington, DC, argued for plaintiffs-appellants. With him on the brief were JOSH A. KREVITT, WAYNE BARSKY, and MICHEAL A. SITZMAN. Of counsel was LUCAS C. TOWNSEND.

JAMES F. HURST, Winston & Strawn LLP, of Chicago, Illinois, argued for defendants-appellees. With him on the brief were DAVID S. BLOCH, CHARLES B. KLEIN, STEFFEN

N. JOHNSON and ANDREW C. NICHOLS. Of counsel was JOHN K. HSU.

Before NEWMAN, DYK, and PROST, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* PROST. Opinion concurring in part and dissenting in part filed by *Circuit Judge* NEWMAN.

PROST, *Circuit Judge.*

Novo Nordisk A/S and Novo Nordisk Inc. ("Novo") appeal a decision of the United States District Court for the Eastern District of Michigan which held that claim 4 of U.S. Patent No. 6,677,358 ("'358 patent") was invalid as obvious and that the '358 patent was unenforceable due to inequitable conduct. *See Novo Nordisk A/S v. Caraco Pharm. Labs.*, 775 F. Supp. 2d 985, 1025 (E.D. Mich. 2011). For the reasons set forth below, we affirm in part and reverse in part.

I. BACKGROUND

This case, now before us for a third time,[1] concerns pharmaceuticals used in the treatment of non-insulin dependent diabetes mellitus ("NIDDM" or "Type II diabetes"), a disease where the body secretes insufficient levels of the hormone insulin, and/or the body is resistant to the effects of insulin. *Id.* at 997. Type II diabetes can be treated with orally administered antidiabetic drugs ("OADs") in the form of monotherapy (a single OAD) or combination therapy (more than one OAD). *Id.* Before the filing date for the '358 patent, there were several

---

[1] *See Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 601 F.3d 1359 (Fed. Cir. 2010), *rev'd*, 132 S. Ct. 1670 (2012), *remanded to*, 688 F.3d 766 (Fed. Cir. 2012).

known classes of OADs having different chemical qualities and varying mechanisms of action. This appeal concerns two of these OAD classes: insulin secretagogues and insulin sensitizers.

Insulin secretagogues work by stimulating insulin release from pancreatic beta cells, and they fall into two subclasses: meglitinides and sulfonylureas. *Id.* at 997-98. As of the '358 patent's filing date, there were five known meglitinides and fifteen known secretagogues, but only a handful of these were generally prescribed for treating Type II diabetes. *Id.* at 997-98, 1004-06. The drug repaglinide, which is a meglitinide, is the primary focus of this appeal.

Insulin sensitizers reduce insulin resistance by acting on the liver to reduce glucose production and thereby improving insulin sensitivity in muscle and fat tissues. *Id.* Of the known sensitizers in the relevant time frame, the most widely-used and successful was a drug called metformin. *Id.* at 1006.

This case involves a claim for treating Type II diabetes with combination therapy using repaglinide and metformin, specifically: "[a] method for treating non-insulin dependent diabetes mellitus (NIDDM) comprising administering to a patient in need of such treatment repaglinide in combination with metformin." *Id.* at 989.

A

Novo, a large pharmaceutical manufacturer, began experimenting in 1990 with repaglinide's efficacy in monotherapy for treating Type II diabetes. *Id.* at 998. It found repaglinide to be a rapid and short-acting insulin secretagogue that was quickly eliminated from the body, findings which corresponded to what was known about the drug in the art. *See id.* at 1004-05. Shortly thereafter, a team of Novo investigators conducted a study on Australian patients to determine whether repaglinide

might be more effective when administered in combination therapy with metformin ("Moses Study").

In the Moses Study, patients failing on metformin alone were given repaglinide/metformin combination therapy. *Id.* at 1010. One of Dr. Moses's test parameters, HbA1c or glycosylated hemoglobin, measured the patient's average glucose level in the recent past. *Id.* The repaglinide/metformin combination reduced that level by 1.41%, or roughly twice what repaglinide and metformin separately yielded in monotherapy. *Id.*

The Moses Study also measured fasting plasma glucose ("FPG") levels, which is the glucose level after the patient has not eaten for about eight hours. *Id.* Although repaglinide was previously thought to have no effect upon FPG due to its short-acting tendencies, the Moses Study found that repaglinide/metformin reduced FPG to levels more than eight times lower than what was typically achieved by metformin alone. *Id.*

Armed with the results from its Moses Study, Novo filed a provisional patent application for the repaglinide/metformin combination on October 29, 1997. *Id.* at 999. The examiner rejected this initial application, reasoning that it was obvious to try combining repaglinide with metformin, and it was also predictable that the combination would yield, at a minimum, a benefit equal to the drugs taken separately, i.e., an "additive" effect.[2] *Id.* at 999-1000.

---

[2] Combination therapy yields an "additive" effect when the total effect of the combination equals the sum of the effect of each drug taken separately, and a "synergistic" effect when the combination's effect exceeds the sum of the separately administered effects. *Novo Nordisk*, 775 F. Supp. 2d at 998.

Novo responded by directing the examiner's attention to Example 3 of its application, which contained the data from the Moses Study, and arguing that this study yielded synergistic results which no artisan would have expected. *Id.* at 1000. The examiner disagreed, and continued her rejection. *Id.* Novo's third and fourth office action responses, each of which asked the examiner to reconsider her position on the Moses Study, were both rejected. *Id.*

Novo then filed a fifth response, this time presenting via declaration the results of an additional study conducted by Novo scientist Dr. Sturis ("Sturis Declaration"). *Id.* at 1000-01. Dr. Sturis's study tested the effects of metformin and repaglinide on the glucose levels of "Zucker obese rats," which are rats bred specifically for use in pharmaceutical studies as models for obesity, diabetes and heart disease. *Id.* at 1000 n.10. Dr. Sturis divided twenty rats into four groups: the first group was given a placebo, the second was given only metformin, the third was given only repaglinide, and the fourth was given the repaglinide/metformin combination therapy. J.A. 17167. Dr. Sturis measured the blood glucose levels of these rats at 30, 60, and 120 minutes, and then calculated the combination's "hypothetical additive effect" by adding the glucose reduction found in the metformin-only rats to that of the repaglinide-only rats. J.A. 17168. Finally, he compared the "hypothetical additive effect" to the actual glucose reduction found in the repaglinide/metformin group to calculate the probability (as a "p-value"[3]) that

[3] The p-value is a value that statisticians use to show the level of uncertainty in a study's results. *Novo Nordisk*, 775 F. Supp. 2d at 1018 n.20. A p-value is "statistically significant" if it is 0.05 or less, which indicates that there is 5% or less likelihood that the outcome was the result of pure chance. *Id.*

any glucose reduction caused by the combination therapy might be attributable to synergistic rather than additive effects. *Id.*

Dr. Sturis reported his study's results in two ways. First, he plotted a chart showing glucose levels across time and then calculated the "area under the curve" for each line, thus expressing the average glucose reduction found across the entire study for each group of rats. J.A. 17168. According to this calculation, the rats who received the repaglinide/metformin treatment experienced a greater average reduction in blood glucose levels than the other three groups, and the combination therapy also proved more effective than the "hypothetical additive effect" of the two drugs. *Id.* The p-value for this finding was 0.061. *Id.* Second, Dr. Sturis isolated just the glucose measurements taken at the 120-minute mark, where he found the largest disparity between repaglinide/metformin and the other three groups. J.A. 18169. Using this data, he calculated a p-value of 0.02. *Id.*

Dr. Sturis opined that the 0.061 p-value "indicate[d]" that repaglinide/metformin had a synergistic effect upon blood glucose levels over the entire two-hour span, and that the 0.02 p-value at the 120-minute mark in particular demonstrated "significant synergy." J.A. 17168-69. He thus concluded that repaglinide/metformin combination therapy had synergistic effects in Zucker obese rats, and that his study together with the Moses Study "strongly suggest[ed] that the combination of repaglinide and metformin has synergistic properties in type 2 diabetic [human] patients." *Novo Nordisk*, 775 F. Supp. 2d at 1019.

Novo submitted the Sturis Declaration to the examiner, along with assertions from its counsel Dr. Richard Bork that the declaration "provide[d] clear evidence of synergy . . . in the treatment of type II diabetes," and that

any prima facie case of obviousness was "rebutted by the evidence of synergistic and surprising results achieved by the claimed combined therapy in humans." *Id.* at 1001.

The examiner withdrew her rejection, explaining that her decision was "[b]ased solely upon the Declaration submitted by Dr. Sturis and reconsideration of the synergistic effects demonstrated in Example 3." *Id.* at 1001. After additional proceedings not relevant here, the '358 patent issued on January 13, 2004. *Id.* Claim 4 of the patent, which is the sole claim at issue here, was not amended at any point during prosecution. *Id.*

B

The present litigation arose under the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98–417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. §§ 355, 360cc; 35 U.S.C. §§ 156, 271), as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108–173, 117 Stat. 2066 (2003) (collectively, "Hatch-Waxman Act"). Specifically, this case stems from an Abbreviated New Drug Application that Caraco filed in 2005 requesting approval from the Food and Drug Administration to sell a generic version of repaglinide, which the Orange Book associated with Novo's '358 patent.[4] Caraco certified in the filing that the '358 patent was invalid or would not be infringed by the sales of the generic repaglinide, and Novo responded with a patent infringement lawsuit claiming that Caraco infringed claim 4 of the '358 patent. Caraco counterclaimed asserting, inter alia, obviousness and unenforceability. *Novo Nordisk*, 775 F. Supp. 2d at 989.

---

[4] For more details about the pharmaceutical applications that inspired this case, or about the history, language, and scope of the Hatch-Waxman Act, *see Caraco*, 132 S. Ct. at 1675-80.

Following a bench trial, the district court held that claim 4 of the '358 patent was invalid because of obviousness and that the patent was not enforceable because of inequitable conduct. Novo appeals these rulings, and we have jurisdiction under 28 U.S.C. §§ 1292(c)(2) and 1295(a).

II. OBVIOUSNESS

We turn first to the district court's obviousness ruling. The district court found, and the parties do not dispute, that Caraco set forth a prima facie case that it was obvious to try combination therapy using metformin and repaglinide to treat Type II diabetes. *Novo Nordisk*, 775 F. Supp. 2d at 1007. It was apparently well-known in the art that two drugs having different mechanisms for attacking diabetes may be more effective than one, and so drugs were often tested in combination therapy after demonstrating effectiveness in monotherapy. *Id*. at 1002. Combination therapy using insulin sensitizers and insulin secretagogues was common at the time, and metformin was the most widely-used insulin sensitizer as of the '358 patent's filing date. *Id*.

Having thus established the existence of a prima facie case, but "[b]efore reaching the ultimate conclusion on the issue of obviousness," the district court undertook a thorough analysis of "the evidence and assertions of unexpected and surprising results, as well as synergistic results." *Id*. at 1007. The key question was whether repaglinide/metformin proved more effective than what would have been expected in view of the prior art, i.e., whether the combination yielded an unexpected synergistic effect.

To undermine the examiner's finding that the Moses and Sturis studies had demonstrated synergy, Caraco introduced new prior art and evidence which the examiner had never considered, such as testimony from expert witnesses and Novo scientists. *Id*. at 1009. After review-

ing Caraco's evidence, the district court determined that an artisan would have expected repaglinide/metformin would yield some synergy. *Id.* at 1010. The court then considered, and rejected, the premise that Novo's studies had yielded an unexpected or superior level of synergy, finding instead that Novo's results were entirely expected in view of the state of the art at that time. *Id.* at 1017. The court thus concluded that Caraco had shown, by clear and convincing evidence, that claim 4 of the patent was invalid as obvious. *Id.* at 1018.

Novo attacks the district court's obviousness ruling on three grounds. First, it asserts that the district court misallocated the burden of persuasion in this case by forcing Novo to "overcome" Caraco's "prima facie" case of obviousness with evidence of unexpected results. Second, Novo argues that even if the burdens were properly allocated in this case, Caraco's evidence insufficiently supported the court's ultimate obviousness findings. Finally, Novo believes that the district court should have deferred to the examiner's original finding that the Sturis and Moses studies demonstrated unexpected synergy.

For the reasons set forth below, we disagree with all three of Novo's arguments, and we therefore affirm the district court's conclusion that claim 4 of the '358 patent is invalid as obvious.

A

As its first ground for reversal, Novo contends that the district court misallocated the burden of persuasion during its obviousness analysis. It is black-letter law that a patent is presumed valid under 35 U.S.C. § 282, that a party challenging its validity bears the burden of proving the factual elements of invalidity by clear and convincing evidence, and that "because the presumption of validity remains intact . . . throughout the litigation," the burden of persuasion never shifts to the patentee during the

course of a district court obviousness challenge. *Pfizer v. Apotex*, 480 F.3d 1348, 1359-60 (Fed. Cir. 2007).

In this case, the district court recited the correct legal standard for obviousness, stating that:

> [o]nce the challenger has presented a prima facie case of invalidity, the patent owner has the burden of going forward with rebuttal evidence. This requirement "does not in substance shift the burden of persuasion, because the presumption of validity remains intact and *the ultimate burden of proving invalidity remains with the challenger throughout the litigation*."

Novo Nordisk, 775 F. Supp. 2d at 992 (emphasis added) (quoting *Pfizer*, 480 F.3d at 1359-60).

Novo concedes that the district court correctly summarized the law of obviousness, but insists that the court misapplied this law in practice. Novo focuses upon language the court uses throughout its opinion, for instance, the court's ultimate obviousness conclusion that "[Caraco's] strong prima facie case of obviousness has not been *overcome* by Novo's *attempt to prove* unexpected results and commercial success." *Id.* at 1018 (emphases added). Novo cites this language as evidence that the court adopted an erroneous burden-shifting approach, similar to the one we recently rejected in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063 (Fed. Cir. 2012).

In *Cyclobenzaprine*, we reversed and vacated a district court decision where the court reached its ultimate conclusion on obviousness based solely upon the prima facie evidence. *Id.* at 1075 (the prematurity of the district court's obviousness conclusion was apparent because "[i]t was not until after the district court found the asserted claims obvious that it proceeded to analyze the objective considerations"). In so doing, we reaffirmed our

longstanding precedent that it is error to find a claim obvious "before . . . consider[ing] the objective considerations," or to shift the burden of persuasion to the patentee at any point during its obviousness analysis. *Id*. at 1075.

Novo argues that just as in *Cyclobenzaprine*, the district court here reached its ultimate obviousness conclusion based solely upon Caraco's prima facie evidence, then shifted the burden of persuasion onto Novo. It believes that this must have been so, because the court considered whether Novo had "overcome" Caraco's evidence by "attempt[ing] to prove unexpected results." *Novo Nordisk*, 775 F. Supp. 2d at 1018.

Novo misinterprets the role of the burden of persuasion in patent litigation. As noted above, the burden of persuasion remains with the challenger during litigation because every issued patent is entitled to a presumption of validity. However, the presumption of validity does not relieve the patentee of any responsibility to set forth evidence in opposition to a challenger's prima facie case which, if left unrebutted, would be sufficient to establish obviousness. Rather, the presumption of validity conveys two distinct advantages upon a patentee in the litigation context.

The patentee's first advantage is a procedural one—he is required to come forward with evidence of non-obviousness only after the challenger has successfully made his prima facie case demonstrating that the patent might be obvious. *See, e.g., Pfizer*, 480 F.3d at 1360 ("[O]nce a challenger has presented a prima facie case of invalidity, the patentee has the burden of going forward with rebuttal evidence."); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed. Cir. 1983). This benefit relates to the burden of production, which initially lies with the challenger, then shifts to the patentee during the course of the litigation.

The patentee's second advantage is a substantive one—he prevails on the issue of validity unless the challenger proves to the decisionmaker by a clear and convincing standard that, after all of the evidence has been placed on the table for consideration, the claim is invalid. *See, e.g., Pfizer*, 480 F.3d at 1360; *Stratoflex*, 713 F.2d at 1534. This benefit relates to the burden of persuasion, and as we have often held (most recently in *Cyclobenzaprine*), this burden never shifts during the course of the litigation.

In this case, the court found that Caraco's prima facie evidence, if unrebutted, would be sufficient to establish that the repaglinide/metformin combination was obvious to try, and that a person of ordinary skill in the art would have reasonably expected the combination would yield success in the form of beneficial, and even synergistic, results. *Novo Nordisk*, 775 F. Supp. 2d at 1006-07, 1010. Having so found, it was entirely appropriate for the court to next consider whether Novo's countervailing secondary consideration evidence of unexpected synergy (i.e., its "attempt to prove unexpected results") was sufficient to "overcome" Caraco's prima facie case. The mere fact that the court conducted this analysis using terms such as "overcome" and "prima facie" does not necessarily imply that it shifted the burden of persuasion onto Novo. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 426 (2007) ("Like the District Court, finally, we conclude Teleflex has shown no secondary factors to *dislodge* the determination that claim 4 is obvious.") (emphasis added) (affirming *Teleflex Inc. v. KSR Int'l Co.*, 298 F. Supp. 2d 581, 596 (E.D. Mich. 2003) ("[T]he Court finds the evidence of commercial success insufficient to *overcome* Defendant's clear and convincing evidence of obviousness.") (emphasis added)); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1365 n.5 (Fed. Cir. 2012) ("[U]se of the terms 'prima facie' and 'rebuttal' in addressing an invalidity challenge does not constitute reversible error as

long as the court 'consider[s] *all* evidence of obviousness and nonobviousness before reaching a determination' and does not shift the burden from the patent challenger.") (citing *In re Cyclobenzaprine*, 676 F.3d at 1077). Rather, as long as the court reserved its ultimate conclusion on validity until after it considered the evidence from both sides, this language simply reflects the court's shift of the burden of production once the court determined that the challenger has established a prima facie case of obviousness.

Nothing in the court's opinion in this case indicates that it reached a premature conclusion on obviousness. To the contrary, after considering the prima facie evidence but "*[b]efore reaching the ultimate conclusion on the issue of obviousness*," the court thoroughly evaluated all evidence of unexpected synergy and commercial success. *See Novo Nordisk*, 775 F. Supp. 2d at 1007 (emphasis added); *id*. at 1007-1017. It then concluded that, in view of all of this evidence, Caraco had shown by clear and convincing evidence that the combination was obvious. *Id*. at 1018. Therefore, the court's analysis was entirely appropriate under *Cyclobenzaprine* and the rest of our obviousness law.

Furthermore, and in any event, the district court did not invalidate claim 4 due to Novo's failure to prove unexpected results, as Novo alleges. Instead, it found that Caraco had established by "[c]lear and convincing evidence . . . that the results of the claimed combination therapy said by Novo to be unexpected and unexplainable were, to the contrary, *expected and explainable* in light of the state of the art as of the critical date." *Id.* (emphasis added). The nature of this finding further undercuts Novo's claim that the burden of persuasion shifted during the course of the opinion.

We therefore reject Novo's contention that the district court misallocated the burden of persuasion, and decline to reverse on this basis.

B

Novo next argues that even if the district court correctly allocated the burden of persuasion for obviousness, the record evidence did not support a conclusion of expected results. On appeal from a bench trial on obviousness, we review de novo the court's the ultimate legal conclusion of whether a claimed invention would have been obvious, and review the underlying findings of fact for clear error. *See Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004).

At trial, Caraco contended that an artisan seeking to predict the performance of repaglinide combined with metformin would have considered metformin's history in combination therapy with other insulin secretagogues, particularly those in the sulfonylurea class. Caraco presented evidence, including some prior art and testimony never before the examiner, which indicated that earlier metformin/sulfonylurea combinations were generally understood to yield synergy. Based upon this evidence, Caraco argued that artisans would have expected repaglinide to be likewise synergistic when combined with metformin.

Novo countered that expectations for the repaglinide/metformin combination would have been instead based primarily, if not exclusively, upon repaglinide's known efficacy in monotherapy. Novo's evidence indicated that repaglinide was known to be a short-acting insulin secretagogue, different from the longer-acting sulfonylureas in Caraco's prior art. Novo specifically relied upon a study by Wolffenbuttel which showed that repaglinide in monotherapy had no impact upon patient FPG. Based upon Wolffenbuttel, Novo insisted that an artisan would have been very surprised when repaglinide/metformin

proved to be eight times more effective in reducing FPG levels than metformin alone.

The district court agreed with Caraco, applying the following three-step reasoning:

> (1) the closest prior art [to the repaglinide/metformin combination] was combination therapy using metformin and a sulfonylurea;
>
> (2) combination therapy using metformin and one of the sulfonylurea class of secretagogues was well known in the art to produce beneficial and even synergistic results in controlling glucose levels in Type II diabetes patients; [and]
>
> (3) repaglinide was known as an insulin secretagogue having a similar mechanism of action to the sulfonylurea class of secretagogues.

Novo Nordisk, 775 F. Supp. 2d at 1010. We see no clear error in these findings. Repaglinide and sulfonylureas are both insulin secretagogues, and they therefore have a "similar mechanism of action" in that they both treat diabetes by stimulating the pancreas to release insulin. *Id.* at 997. Metformin is an insulin sensitizer, which treats diabetes patients using a different mechanism, i.e., by reducing their resistance to insulin. *Id.* Furthermore, the prior art taught that metformin could be combined with certain sulfonylureas which were, like repaglinide, short-acting secretagogues. *Id.* at 1005. It is reasonable that an artisan seeking to combine a known insulin sensitizer (like metformin) with a new insulin secretagogue (like repaglinide) would base his expectations upon prior art sensitizer/secretagogue combinations.

In view of these findings, it was not erroneous for the court to conclude that the prior art predicted the results found in the Moses Study. For example, the near-term and long-term benefits which Dr. Moses observed in his repaglinide/metformin study were generally inferior to

the results found by prior art studies involving metformin combined with sulfonylureas. *See id.* at 1011-12. Novo argues that these studies tell only half the tale, because they fail to account for the differences between sulfonylureas and repaglinide in monotherapy. But other trial evidence also supports the district court's conclusion—for instance, Dr. Sturis testified that he originally declined to sign a declaration supporting Novo's application because he felt that Dr. Moses had not mathematically or scientifically proven the existence of synergy. *See id.* at 1019.

Dr. Sturis did, of course, eventually submit a declaration on Novo's behalf. But he only did so after conducting his own study, and even then, he went only so far as to state that the evidence "strongly suggest[ed]" synergy. *Id.* It was not clearly erroneous for the district court to find that Dr. Sturis's results were expected, given that his conclusions mirror the conclusions drawn in Caraco's new sulfonylurea prior art, which also suggested the existence of synergy. *Id.* at 1009 (citing prior art reports that metformin/sulfonylurea combinations yielded an "apparent synergistic effect" and "appear[ed] to have a synergistic effect").

The only other study that supposedly demonstrated unexpected results was a study conducted by Pfeiffer, which compared the insulin sensitivity of eleven patients taking only metformin with that of the same patients after taking the repaglinide/metformin combination. *Id.* at 1014. Novo argued that no ordinary artisan would have expected the results that Pfeiffer observed, namely, a 35% improvement in insulin sensitivity in combination therapy over what was seen when the patients took metformin alone. *Id.* But Caraco's expert questioned that study's reliability due to its small sample size, and also pointed out that Pfeiffer had himself explained away his results in a contemporaneous report as predictable in view of the prior art. *Id.*

The court further noted that certain tests conducted upon different classes of patients yielded results that contradicted those found by Moses, Sturis, and Pfeiffer. For instance, in one test where half of the patients were "drug-naïve" (i.e., they had never before used any OADs), "the synergistic effect of combination therapy observed by Moses et al[.] was not consistently seen." *Id.* at 1016. In another study, where all of the patients involved were drug-naïve, the combination therapy did not show statistically better results than the drugs used in monotherapy. *Id.*

In view of all of these findings, few of which are challenged by Novo as clearly erroneous,[5] Caraco proved by clear and convincing evidence that an artisan would have expected the level of synergy Novo found when it combined metformin and repaglinide. We therefore decline to reverse the district court's obviousness determination on this basis.

---

[5] Novo does challenge as clearly erroneous the district court's finding that repaglinide/metformin combination therapy had not been commercially successful, a conclusion the court reached based upon evidence and testimony that doctors seldom prescribe the combination to treat Type II diabetes. *Novo Nordisk*, 775 F. Supp. 2d at 1017. Novo argues that the repaglinide/metformin combination was much more commercially successful than repaglinide alone, and that most repaglinide sales today are for use in combination therapy with metformin. However, the most probative evidence of commercial success is not overall sales, but whether those sales represent "a substantial quantity in th[e] market." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1300 (Fed. Cir. 2012) (citing *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996)). Thus, the district court's finding was not clearly erroneous.

C

Lastly, Novo contends that the district court should have deferred to the examiner's finding that the Moses and Sturis studies demonstrated synergy. Novo's theory cites the recent case *Kappos v. Hyatt*, where the Supreme Court held that, in cases involving district court review of U.S. Patent and Trademark Office ("PTO") rejections under 35 U.S.C. § 145, new evidence may be considered and that "it makes little sense for the district court to apply a deferential standard of review to PTO factual findings that are contradicted by the new evidence." *Kappos v. Hyatt*, 132 S. Ct. 1690, 1696 (2012). Novo inverts this statement, and argues that if evidence presented at trial is *not* new evidence then the district court *must* defer to the findings of the examiner. Because Novo believes that all of Caraco's prior art was merely cumulative of what was already before the examiner, it concludes that de novo fact-finding was not justified in this case.

Hyatt has no relevance here. *Hyatt* concerned 35 U.S.C. § 145, which provides for optional review in the Eastern District of Virginia of decisions from the PTO rejecting patent applications in the first instance. 35 U.S.C. § 145; *Hyatt*, 132 S. Ct. at 1694. The present case is a district court challenge to an issued patent brought under the Hatch-Waxman Act, not a challenge to a PTO rejection brought under § 145, and *Hyatt* is therefore irrelevant. But in any event, in cases such as this we do not review the PTO's decision. 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.

III. INEQUITABLE CONDUCT

We next address the district court's determination that the '358 patent was unenforceable due to inequitable conduct. We review the district court's ultimate finding of inequitable conduct for abuse of discretion, and review the underlying findings of materiality and intent for clear error. *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1291 (Fed. Cir. 2011) (en banc); *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1374-76 (Fed. Cir. 2007).

At trial, Caraco alleged that the Sturis Declaration, as well as the representations made by Dr. Bork during prosecution of the '358 patent, constituted inequitable conduct. In particular, Caraco challenged: (a) Dr. Sturis's omission of certain opinions regarding his own study and the Moses Study, as well as his failure to tell the PTO that certain of his reported results had not been part of his original test protocol; and (b) Dr. Bork's assertion that Dr. Sturis's data provided "clear evidence of synergy," and his failure to disclose certain e-mails that allegedly refuted this statement. *Novo Nordisk*, 775 F. Supp. 2d at 1019, 1021. These actions were particularly troubling, Caraco contended, because the examiner withdrew her rejection "[b]ased solely upon the Declaration submitted by Dr. Sturis and reconsideration of the synergistic effects." *Id.* at 1001.

The district court issued its opinion after we agreed to hear *Therasense* en banc, but before we reached our decision in that case. Therefore, it applied both the pre-*Therasense* and post-*Therasense* tests for materiality and intent, and found that under either standard, Sturis and Bork had intentionally withheld material information

from the PTO. *See id.* at 995, 1021-22. Accordingly, the court concluded that the '358 patent was unenforceable due to inequitable conduct. *Id.* at 1024.

Novo argues that the district court clearly erred in finding that Sturis's and Bork's representations and omissions were material and intentional under *Therasense*. We agree with Novo on the issue of materiality, and so for the reasons outlined below, we reverse the district court's conclusion on inequitable conduct.

A

Caraco's inequitable conduct case against Dr. Sturis was based upon his trial testimony, wherein he conceded certain facts that were never submitted to the PTO. For instance, Dr. Sturis testified that when he first conducted his study, he had planned to calculate only one p-value based upon the "area under the curve" data, which resulted in a p-value of 0.061. But after conducting his test, he decided to calculate and submit the second p-value (i.e., the 0.02 p-value) using the isolated data from the 120-minute interval. *See id.* at 1019-20. Dr. Sturis's Declaration did not indicate to the PTO that his original test protocol called for calculating only the less favorable of the two p-values he ultimately presented.

Dr. Sturis also testified that his rat study, having been conducted on animals, could not alone establish that the combination had a synergistic effect on humans. *Id.* at 1021. He further told the court that he held reservations, both before and after submitting his Declaration, about whether the Moses Study alone, or even taken together with the results of his rat study, could affirmatively prove synergy in humans. *Id.* at 1020-21.

Based upon this testimony, the district court found that Dr. Sturis had omitted material information from his Declaration, namely:

> the facts that the two-hour data point was not part of the test protocol, and that a correction factor had not been applied to that p-value. That data point was the only one in his rat test that appeared to produce a statistically significant p-value of less than 0.05. Also undisclosed were Sturis' opinions . . . that, by his own standards requiring mathematical proof, neither his rat study nor the Moses Study alone proved synergy in humans.

Id. at 1020. The omissions were material under the pre-*Therasense* standard, the court found, "because they refuted or were inconsistent with the opinions expressed in his Declaration in support of patentability" and because "[a] reasonable examiner, focused on the issue of synergism as was the examiner here, would have wanted to consider any qualifications or reservations held by Sturis concerning the conclusions he expressed in his Declaration." *Id.* at 1021. The court further found that "the examiner's explicit reliance on the Sturis Declaration warrants the conclusion that the Declaration satisfied the [post-*Therasense*] 'but for' materiality test." *Id.*

We reject the district court's materiality finding as clearly erroneous, because we fail to see how Dr. Sturis's omissions qualify as "but for" material. For instance, any reasonable examiner would have understood that Dr. Sturis's rat study was conducted on animals, and therefore could not definitively prove synergy in humans. Moreover, Dr. Sturis's declaration, which stated only that his results "indicated" and "strongly suggest[ed]" synergy, was generally consistent with his trial testimony that synergy was not affirmatively proven and that "neither his rat study nor the Moses Study alone proved synergy in humans." *Id.* at 1020.

While Dr. Sturis's decision to omit his original test protocol from the Declaration is slightly more troubling, it

similarly fails the "but for" materiality test. This is not a case where a declarant hid adverse test results from the PTO in favor of more promising data selected post hoc. Here, Dr. Sturis disclosed the results of his original protocol to the examiner, allowing her the opportunity to weigh the significance of the different p-values he calculated. Nor is this a case where the declarant's omission expressly undermined his stated opinion. To the contrary, even after taking the omitted test protocol into account, the court specifically found that Dr. Sturis's conclusions on synergy had not been shown to be false. *See id.* ("[Dr. Sturis's 'strongly suggests' qualified conclusion] has not been shown by clear and convincing evidence to be false.")

Instead, Dr. Sturis stands accused of inequitable conduct because he failed to notify the PTO that the 0.02 p-value calculated at 120 minutes, while probative of synergy, was not called for in his original test plan. Although this information ideally would have been disclosed to the PTO, it is nevertheless a non-material omission because it can "be rendered irrelevant in light of subsequent argument or explanation by the patentee." *See Therasense*, 649 F.3d at 1294. For instance, at trial, Dr. Sturis justified his deviation from protocol by testifying that he saw surprisingly high levels of glucose reduction at 120 minutes, and he felt it would have been scientifically irresponsible for him not to investigate and report those findings. In view of this reasonable explanation, and the fact that he disclosed the results of his original test protocol to the PTO, we do not believe that his omitted test protocol was "but for" material.

B

Caraco's inequitable conduct case against Dr. Bork focused primarily upon the following statements he made in support of the Sturis Declaration:

> the data presented in the Declaration of Dr. Sturis, provides *clear evidence of synergy* for the use of the claimed combination of repaglinide and metformin in the treatment of type II diabetes.
>
> . . . prima facie case [of obviousness] is rebutted by the evidence of *synergistic and surprising results* achieved by the claimed combination therapy in humans (Example application) and in Zucker obese rats (Sturis' Declaration).

Novo Nordisk, 775 F. Supp. 2d at 1021 (alteration in original). The district court found that this statement was material because it went beyond Sturis's "strongly suggests" language by indicating that "clear evidence" of "synergistic and surprising results" in humans had been "achieved."

Caraco also alleged that Dr. Bork should have provided the PTO with an e-mail he received from Dr. Sturis after making the above representations, wherein Dr. Sturis stated that "[t]he presence of greater-than-additive effects *may* be of relevance to the clinical efficacy of the [repaglinide/metformin] combination." *Id.* at 1022 (emphasis added). The court found that Bork should have understood that the word "may" contradicted his prior representation that "clear evidence" of synergy in humans had been "achieved," and that this triggered his duty to disclose the e-mail.

The court deemed Bork's representations material under the pre-*Therasense* standard because his unqualified statements contradicted with what he knew about the Sturis Declaration, i.e., that it did not definitively prove synergy. *Id.* The district court addressed the post-

Therasense test only briefly, stating that "[a]s in the case of the Sturis Declaration, [Dr. Bork's representations] also satisfy the alternative 'but for' materiality test." *Id.*

As with Dr. Sturis's omissions, we believe that the statements and omissions by Dr. Bork are troubling, but not material. Dr. Bork's characterization of the Sturis Declaration employed carefully-chosen language which tracked the qualified nature of Dr. Sturis's opinions. For instance, whereas Dr. Sturis said his results "indicated" and "strongly suggest[ed]" synergy, Dr. Bork referred to Sturis's test results as "evidence" rather than "proof" of synergy. These statements are also generally consistent with Dr. Sturis's e-mail, and its use of the word "may."

We therefore reverse the district court's materiality and inequitable conduct findings as to both Dr. Sturis and Dr. Bork. We need not reach the issue of intent.

IV. CONCLUSION

For the reasons set forth above, we affirm the district court's determination that claim 4 of the '358 patent was invalid as obvious, but reverse the district court's determination that the '358 patent was unenforceable due to inequitable conduct.

AFFIRMED IN PART AND REVERSED IN PART

United States Court of Appeals for the Federal Circuit

NOVO NORDISK A/S AND NOVO NORDISK INC.,
Plaintiffs-Appellants,

v.

CARACO PHARMACEUTICAL LABORATORIES, LTD. AND SUN PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Appellees.

2011-1223

Appeal from the United States District Court for the Eastern District of Michigan in No. 05-CV-40188, Judge Avern Cohn.

NEWMAN, *Circuit Judge*, concurring in part, dissenting in part.

I agree that neither Dr. Sturis nor Dr. Bork engaged in inequitable conduct, and concur in the judgment reversing the district court's ruling in that respect. However, Novo's discovery of the synergistic combination of metformin and repaglinide meets the criteria of patentability, and was incorrectly held to be unpatentable on the ground of obviousness, 35 U.S.C. §103.

The section 103 determination in this case relates to a synergistic combination of two diabetes drugs. The combination described and claimed in the patent in suit, U.S. Patent No. 6,677,358 ("the '358 patent"), is eight-fold

more effective than the additive properties, and is now apparently a treatment of choice for persons whose Type II diabetes had previously been untreatable. It is a life-saving combination for such persons, and is valuable to other diabetics, for it permits a more flexible treatment regimen than prior products. The Novo inventors pursued this combination despite the advice of other "experts" that they were wasting time and money. Nonetheless the district court, and now my colleagues on this panel, find the combination obvious to them, and invalidate the patent. I respectfully dissent.

DISCUSSION

"Real world considerations provide . . . a solid evidentiary foundation on which to rest a nonobviousness determination." *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1575 (Fed. Cir. 1992). These "real world considerations" include the realities and challenges of discovering a new medicinal product. The panel majority discards this principle in concluding that the synergistic combination of metformin and repaglinide would have been obvious to a person of ordinary skill.

The question is not whether it would have been obvious to look for synergistic combinations; the question is whether it was obvious that the combination of metformin and repaglinide would exhibit synergism and that the combination would be 800% more effective than the additive effect of the components separately.

My colleagues reason that because synergism is unpredictable, then if it is found, it is obvious. Maj. Op. at 8. ("It was apparently well-known in the art that two drugs having different mechanisms for attacking diabetes may be more effective than one, and so drugs were often tested in combination."). That is not the meaning of "obvious to try." A new composition is "obvious to try" when it is reasonable to expect that the trial will produce a predict-

able result. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("[T]he fact that a combination was obvious to try might show that it was obvious under § 103" if, among other things, "there are a finite number of identified, predictable solutions"). That situation did not here exist. *See Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.").

It was known that a combination of metformin and a sulfonylurea—a class of compounds that does not include repaglinide—may or may not have a synergistic effect on blood sugar control, for only some sulfonylureas showed such effect. Repaglinide is not chemically similar to the sulfonylureas. It was known at the time of Novo's invention that repaglinide "differs from the sulfonylureas in its molecular structure, profile of action, and excretion mechanism." B.H.R. Wolffenbuttel et al., *Effects of a new oral hypoglycaemic agent, repaglinide, on metabolic control in sulphonylurea-treated patients with NIDDM*, Eur. J. Clin. Pharmacol. 45, 1993, at 113. The existence of synergy in some metformin-sulfonylurea combinations is not predictive of synergy in the combination of metformin with repaglinide.

The defendants deposed the inventors, who explained their thought processes in experimenting with this combination. The district court, and now my colleagues on this panel, cite the testimony of the inventors, who successfully pursued this unpromising combination, and hold that since the inventors pursued this combination and found the observed synergism, the synergism was obvious. The court uses the inventors' exceptional intellect against them, rather than the knowledge of the person of ordinary skill.

The district court held that since these inventors pursued this combination, it was obvious to do so. The court stated that the PTO examiner, in granting the patent on the basis of unpredictable synergy, "did not have the benefit of the testimony of Müller [the inventor] and Damsbo [his colleague] as to the results they expected." *Novo Nordisk A/S v. Caraco Pharm. Labs.*, 775 F. Supp. 2d 985, 1009 (E.D. Mich. 2011). This is a misunderstanding of the law, for "[o]bviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor." *Para-Ordnance Mfg., Inc. v. SGS Importers Int'l, Inc.*, 73 F.3d 1085, 1087 (Fed. Cir. 1995); *see Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed.").

My colleagues adopt the district court's reasoning, ignoring the wisdom counseled by precedent. My colleagues appear to hold that because these Novo scientists studied this combination, it was obvious to try this combination. Such a thesis would expunge patentability for all except random observations. All scientific experiments are conducted with a purpose of inquiry, and all experimenters have a theory of possible outcomes. Such experiments may partake of varying degrees of vision, hope, or expectation on the part of the experimenter, but these are not criteria of patentability.

Patentability is determined not from the position of the inventor, but from the knowledge of the person of ordinary skill. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something . . . which sets them apart from the workers of *ordinary skill*, and one should not go about determining obviousness under § 103 by inquiring into

what *patentees* (i.e., inventors) would have known or would likely have done.") (emphases in original).

For questions of biological synergism, predictability is notoriously difficult. *In re Luvisi*, 342 F.2d 102, 109–10 (CCPA 1965) ("We do not accept the notion that every suggestion of synergism in the art coupled with a finding of synergism in the practice of the invention automatically compels a conclusion of obviousness . . . . [S]ome prior art compositions may show little synergism and others show considerable synergistic effects, with the net result that predictability is impossible save the fact that a synergistic result of some kind will probably be found."); *see also Allergan, Inc. v. Sandoz, Inc.*, ___ F.3d ___, No. 2011-1619, 2013 WL 1810852, at *7 (Fed. Cir. May 1, 2013) (holding combination unobvious because there is "no reason why the success of unrelated drugs would make it obvious to one of ordinary skill that a fixed combination of brimonidine and timolol could be dosed twice per day without loss of efficacy"). My colleagues contravene precedent, and hold that because some synergism has been observed in some combinations with metformin, any discovery of a unique synergistic combination with unusual properties would have been obvious.

The PTO granted this patent based on the synergistic effect that these inventors discovered and established. This activity was not suggested in the prior art, was not predictable, and was not obvious. The court errs in holding otherwise.

A. The Evidence

There was evidence at trial that repaglinide was not successful as an antidiabetic drug:

> Most companies believed that there was no commercial use or value for repaglinide given its pharmacodynamic profile when compared to longer-acting sulfonylureas already on the market or

> other antidiabetics in development. More generally, no one was willing to go to the expense of doing clinical trials for regulatory approval if the drug had no commercial value.

Trial Tr. vol. 9, 14, Aug. 9, 2010 (testimony of Dr. Michael Mark, Novo scientist who conducted research on repaglinide).

Dr. Peter Müller, the inventor of the patent in suit, pressed for clinical trials despite the skepticism of the clinical investigators. Dr. John Miller, Medical Director of Novo in Australia, who coordinated and supervised the Australian study, testified as follows:

> Given that repaglinide was such a short-acting compound that had no effect on FPG [fasting plasma glucose], the investigators tried to explain to the clinical development staff that it made no sense to use fasting glucose as a measurement [because FPG measures] the amount of glucose in blood plasma after the patient has not eaten for about eight hours (i.e., overnight).

Trial Tr. vol. 8, 121–22, Aug. 5, 2010.

The Australian study was conducted with patients with poorly controlled diabetes, who were treated with metformin alone, repaglinide alone, or a combination of metformin and repaglinide. '358 patent col.7 l.61 – col.10 l.40. The patients receiving the combination exhibited markedly better control of blood sugar than either the patients on metformin monotherapy or those on repaglinide monotherapy. *Id.* col.9 ll.37–58. The claimed drug combination's ability to control blood sugar, according to fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA_{1c}) measurements, was substantially better than the additive effects of metformin and repaglinide. *Id.* For example, the combination lowered FPG by 2.18 mmol/l, which was over eight times the efficacy

observed in patients on metformin alone (0.25 mmol/l). *Id.* col.9 ll.45–58. Repaglinide monotherapy actually increased the patients' FPG levels by 0.49 mmol/l, contributing to the problem instead of curing it. *Id.*

Novo scientists were concerned that the Australian study did not prove synergy to a statistical certainty because the study lacked a placebo group. The district court understood that "ethical reasons precluded removing the sick patients from all therapy." *Novo*, 775 F. Supp. 2d at 1010. When the patent examiner criticized Novo's quantification of synergy, Novo conducted the rat study to include untreated controls; the results showed a statistically significant synergistic effect between metformin and repaglinide, corroborating the results of the Australian human study.

The PTO issued the '358 patent on the basis of these studies, stating that "[t]he combined administration of repaglinide and metformin resulted in an unexpected synergistic effect on blood glucose levels." '358 patent "Reasons for Allowance" (May 31, 2003). *See Quad Envtl. Techs. Corp. v. Union Sanitary Dist.*, 946 F.2d 870, 876 (Fed. Cir. 1991) ("[C]ourts may take cognizance of, and benefit from, the proceedings before the patent examiner," although "the question [of validity] is ultimately for the courts to decide, without deference to the rulings of the patent examiner").

The record shows that defendant Sun Pharmaceutical Industries[1] advertises its repaglinide product as synergistic when combined with metformin:

---

[1] Sun is the corporate parent of codefendant Caraco Pharmaceutical Laboratories.

Repaglinide in combination with metformin . . .,

- Produced a greater improvement in glycemic control than that seen by the sum of the changes with the two agents alone.

Undated Advertisement for Rapilin, Sun's Repaglinide Product. This is the benefit that Sun told the district court did not exist. This benefit was unknown until discovered by Novo scientists, and unavailable to public benefit until federally approved at Novo's initiative and expense.

B. Analysis

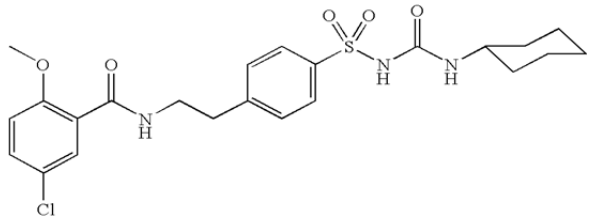
My colleagues misunderstand and misapply the "obvious to try" criterion of obviousness. The motivation to develop a new pharmaceutical "is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made." *In re Gyurik*, 596 F.2d 1012, 1018 (CCPA 1979). This expectation must be rooted in the prior art and in the person of ordinary skill, not in the ingenuity or creativity of the inventor.

The district court reasoned that since metformin was known to form synergistic combinations with some sulfonylureas, it would be obvious to expect synergism of metformin and repaglinide, for although repaglinide is not a sulfonylurea, it was believed to have a similar mechanism of action as a secretagogue. This analysis is supported only by hindsight, for the record reflects a more complicated reality. It was known that synergy is not exhibited by all sulfonylurea secretagogues, and the district court agreed that one skilled in the art would "perhaps" have expected synergistic results from the metformin-repaglinide combination. "Perhaps" is not clear and convincing evidence of obviousness of the unusually efficacious results that were obtained. *See Mi-*

crosoft Corp. v. i4i Ltd. P'ship, 131 S. Ct. 2238, 2242 (2011) (holding that invalidity must be proved by clear and convincing evidence).

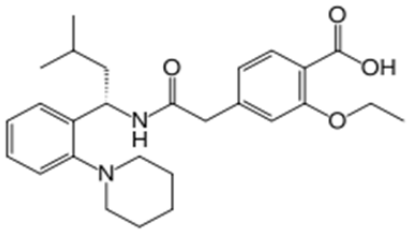
The panel majority offers the generalization that "earlier metformin/sulfonylurea combinations were generally understood to yield synergy." Maj. Op. at 14. This is inaccurate, for only some sulfonylureas formed synergistic combinations. Synergism was not a general property of such combinations. The particular metformin-sulfonylurea combination relied on by the district court to invalidate the '358 patent is metformin-glyburide.[2] The district court observed that both glyburide and repaglinide are "insulin secretagogues" because they stimulate the secretion of insulin. Indeed, this is how most diabetes treatments work. However, it was well-known that not all insulin stimulants form synergistic combinations with metformin.

There are significant differences between glyburide and repaglinide, in structure and in properties. The compounds are structurally quite different:



Glyburide

[2] Glyburide is also known as glibenclamide.



Repaglinide

Glyburide is "long-acting," having a biological half-life of between ten and twenty hours. Repaglinide is "short-acting," with a half-life of about one hour. The record repeatedly states that the short life of repaglinide deterred interest in this compound for treatment of diabetes.

The only prior art of record comparing repaglinide to glyburide, the 1993 Wolffenbuttel article cited *supra,* described the dissimilar effects of the two drugs on blood sugar control in diabetics:

> After 12 weeks glibenclamide [glyburide] had reduced fasting blood glucose levels without any effect on postprandial blood glucose, whereas repaglinide had significantly lowered postprandial blood glucose, but with no effect on fasting blood glucose.

Eur. J. Clin. Pharmacol. 45, at 115. This observation was explained by repaglinide's "mode of action and short plasma half-life." *Id.*

Caraco's expert Dr. Accili conceded at trial that repaglinide would have been expected to have "at best a small impact on fasting plasma glucose." Trial Tr. vol. 4, 52–53, June 7, 2010. This is in contrast to long-acting sulfonylureas such as glyburide, which were known to reduce fasting plasma glucose even absent combination with metformin.

The structural and functional disparities between repaglinide and glyburide render it unreasonable to expect the repaglinide-metformin combination to have synergistic properties superior to the prior art combination of glyburide and metformin. *See In re Lalu*, 747 F.2d 703, 707 (Fed. Cir. 1984) ("[A] relevant property of a compound cannot be ignored in the determination of nonobviousness."). As Dr. Accili acknowledged, "[a]ny time multiple things are used [in combination therapy], the potential for error increases." Trial Tr. vol. 3, 37, June 3, 2010.

The district court did not address the known differences between repaglinide and the sulfonylureas, including glyburide. The court did not mention the Wolffenbuttel article, although it was the only reference to compare repaglinide and a sulfonylurea. In the search for scientific truth "[o]ne cannot . . . pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988); it is necessary to consider prior art that supports unobviousness of the claimed invention, as well as that which weighs against it. *In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991).

The district court's obviousness determination was based on the court's finding that two prior art studies on the metformin-glyburide combination "reported greater reductions in HbA_{1c} and FPG than those of the [Australian] Study." The district court stated that these studies represented the "closest prior art," and invalidated the '358 patent because "[t]he evidence does not establish that the claimed combination therapy produces clinical results superior to those produced by the closest prior art." *Novo*, 775 F. Supp. 2d at 1011–12. That is, the district court held that because the metformin-glyburide combination appeared to control diabetes as well as the metformin-repaglinide combination, the patent was invalid for obviousness. That is not the law of obviousness. *See In re*

Chupp, 816 F.2d 643, 646 (Fed. Cir. 1987) ("To be patentable, a compound need not excel over prior art compounds in all common properties."). Further, the district court did not discuss the evidence of effectiveness in difficult-to-treat cases of Type II diabetes, or other differences that were not predictable from prior art.

The question is whether it would have been obvious that this particular combination would produce results superior to the additive effect of the components separately. It was not shown that because glyburide was an effective synergist, the different compound repaglinide would be expected to be an effective synergist.

The expert witnesses for both sides testified as to the uncertainties of predicting synergistic action. It was not shown that the prior art metformin-glyburide combination predicted the claimed invention, for the differences between glyburide and repaglinide were well-recognized. Glyburide is one of the longer-acting sulfonylureas, a poor comparator for short-acting repaglinide. A more reasonable analysis would consider metformin in combination with nateglinide, which is structurally similar to repaglinide, or a shorter-acting sulfonylurea such as glipizide.

My colleagues state that "the prior art taught that metformin could be combined with certain sulfonylureas which were, like repaglinide, short-acting secretagogues." Maj. Op. at 15. However, the record discussing these short-acting sulfonylurea combinations does not state that their synergy with metformin was known or existed. The "closest prior art" is the reference having the most "in common" with the claimed invention, not the reference that happens to describe the most impressive results. *In re Merchant*, 575 F.2d 865, 868–69 (CCPA 1978); *see KSR*, 550 U.S. at 421 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.").

The purpose of our patent system is a practical one: "To promote the Progress of Science and useful Arts." U.S. Const. art. I, §8, cl. 8. Consistent with this "constitutional command," *Graham v. John Deere Co.*, 383 U.S. 1, 6 (1966), the Supreme Court, and this court, have recognized that the statutory requirement of non-obviousness is a "practical test of patentability," *id.* at 17. Section 103 must be "followed realistically," *id.*, if the law is to support innovation as it is manifested in the pragmatic world of technologic advance and commercial investment. *See KSR*, 550 U.S. at 415 (summarizing the Court's "functional approach" to obviousness); *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (in enacting §103, Congress created "a more practical . . . test for patentability"); *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546 (Fed. Cir. 1984) ("the facts of real-world experience" inform the obviousness analysis); *In re Lunsford*, 357 F.2d 385, 391–92 (CCPA 1966) ("The provisions of section 103 must be followed realistically to develop the factual background against which the section 103 determination must be made.").

The synergy demonstrated by Novo for the metformin-repaglinide combination therapy was not predicted or predictable, and was not obvious.

C. Claim Scope

The district court faulted the Australian study as too narrow to support claims that state that the metformin-repaglinide combination is administered "to a patient in need," a broader class of diabetics than patients whose diabetes is poorly controlled on metformin monotherapy. The district court stated that "Novo presented no evidence that the claimed combination therapy produced unex-

pected or synergistic results in drug-naïve patients."[3] The court concluded that the Australian clinical study and Dr. Sturis' rat study were not probative of synergy "in 'all instances.'" *Novo*, 775 F. Supp. 2d at 1015–17.

Novo's experimentation was objective and substantial. The Australian study was conducted with over eighty persons whose diabetes was poorly controlled on metformin alone, and thus were not "drug naïve." Diabetes is typically treated with a single drug first; if monotherapy does not work, or stops working after a period of time, combination therapy is prescribed. It was reasonable for Novo to test the metformin-repaglinide combination on patients who responded poorly to metformin monotherapy.

Dr. Sturis' rat study corroborated the observed synergism. The district court acknowledged that the Zucker obese rats studied by Dr. Sturis "are an accepted animal model with excellent predictive capabilities for humans with Type II diabetes." *Novo*, 775 F. Supp. 2d at 1013. Novo "demonstrate[d] that an embodiment has an unexpected result and provide[d] an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner, [which] will generally establish that the evidence is commensurate with [the] scope of the claims." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

The Australian study tested, and demonstrated, the efficacy of the metformin-repaglinide combination in a patient population with difficult-to-control Type II diabetes, those who would most benefit from the combination. It was not necessary for Novo to prove synergy in patients for whom combination therapy is not needed, in order to

---

[3] In this context, "drug naïve" refers to a person whose diabetes has not yet been treated pharmaceutically.

claim administering the combination of metformin and repaglinide to "a patient in need." *See In re Chupp*, 816 F.2d at 646 (to be patentable, a compound need not "produce superior results in every environment in which the compound may be used"); *In re Kao*, 639 F.3d at 1068 (a patentee is not obligated "to test every embodiment within the scope of the claims").

From my colleagues' erroneous view of the evidence and incorrect application of the law of obviousness, I respectfully dissent.