United States Court of Appeals for the Federal Circuit

SANOFI-AVENTIS U.S., LLC, SANOFI MATURE IP, SANOFI,
Plaintiffs-Appellants

v.

DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., SANDOZ, INC.,
Defendants-Appellees

FRESENIUS KABI USA, LLC, ACCORD HEALTHCARE, INC., APOTEX CORP., APOTEX INC., ACTAVIS LLC, ACTAVIS ELIZABETH LLC, MYLAN LABORATORIES LIMITED,
Defendants-Cross-Appellants

2018-1804, 2018-1808, 2018-1809

Appeals from the United States District Court for the District of New Jersey in Nos. 3:14-cv-07869-MAS-LHG, 3:14-cv-08079-MAS-LHG, 3:14-cv-08082-MAS-LHG, 3:15-cv-00287-MAS-LHG, 3:15-cv-00290-MAS-LHG, 3:15-cv-00776-MAS-LHG, 3:15-cv-01835-MAS-LHG, 3:15-cv-02520-MAS-LHG, 3:15-cv-02522-MAS-LHG, 3:15-cv-02631-MAS-LHG, 3:15-cv-03107-MAS-LHG, 3:15-cv-03392-MAS-LHG, 3:16-cv-02259-MAS-LHG, 3:16-cv-05678-MAS-LHG, Judge Michael A. Shipp.

Decided: August 14, 2019

WILLIAM E. SOLANDER, Venable LLP, New York, NY, argued for plaintiffs-appellants. Also represented by KATHERINE ADAMS, DOMINICK A. CONDE, WHITNEY LYNN MEIER, DANIEL JOHN MINION.

EMILY L. RAPALINO, Goodwin Procter LLP, Boston, MA, argued for all defendants-cross-appellants. Defendants-cross-appellants Fresenius Kabi USA, LLC, Actavis LLC, Actavis Elizabeth LLC also represented by DARYL L. WIESEN, ERIC ROMEO; AVIV ZALCENSTEIN, New York, NY.

ANDREW M. ALUL, Taft, Stettinius & Hollister, LLP, Chicago, IL, argued for all defendants-cross-appellants. Defendants-cross-appellants Apotex Corp., Apotex Inc. also represented by ROSHAN SHRESTHA.

FRANK RODRIGUEZ, Windels Marx Lane & Mittendorf LLP, Madison, NJ, for defendants-appellees Dr. Reddy's Laboratories, Inc., Dr. Reddy's Laboratories, Ltd. Also represented by JAMES BARABAS.

LAURA A. LYDIGSEN, Brinks Gilson & Lione, Chicago, IL, for defendant-appellee Sandoz, Inc. Also represented by MARK HERBERT REMUS, JOSHUA JAMES.

IMRON T. ALY, Schiff Hardin, Chicago, IL, for defendant-cross-appellant Accord Healthcare, Inc. Also represented by HELEN H. JI.

MATTHEW R. REED, Wilson, Sonsini, Goodrich & Rosati, PC, Palo Alto, CA, for defendant-cross-appellant Mylan Laboratories Limited. Also represented by WENDY L. DEVINE, KRISTINA M. HANSON, San Francisco, CA.

Before LOURIE, MOORE, and TARANTO, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Plaintiffs-Appellants (collectively, "Sanofi") appeal from the judgment of the U.S. District Court for the District of New Jersey holding, after a bench trial, claims 7, 11, 14–16, and 26 of U.S. Patent 8,927,592 (the "'592 patent") invalid as obvious. *Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC*, No. 14-7869 (D.N.J. Dec. 19, 2017) ("*Decision*"). Defendants-Cross-Appellants (collectively, "Fresenius") cross-appeal from the same judgment holding claims 1 and 2 of U.S. Patent 5,847,170 (the "'170 patent") not invalid as obvious. Because there was no case or controversy with respect to claims 7, 11, 14–16, and 26 of the '592 patent when the district court issued its decision, we vacate the court's decision concerning those claims. We affirm the court's judgment that the '170 patent is not invalid as obvious.

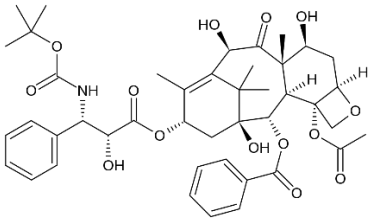
BACKGROUND

Sanofi owns the '170 and '592 patents, respectively claiming the compound cabazitaxel and methods of using it. Sanofi markets cabazitaxel under the trade name Jevtana® to treat certain drug-resistant prostate cancers. Both the '170 and '592 patents are listed in the Orange Book[1] as covering cabazitaxel.

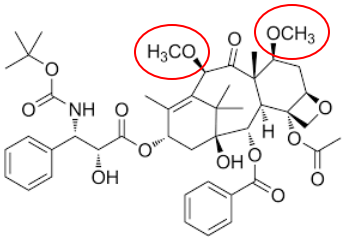
Cabazitaxel belongs to a family of compounds called taxanes and is the third and most recent taxane drug to gain approval by the Food and Drug Administration ("FDA"). The other two are paclitaxel, approved in 1992, and docetaxel, approved in 1996. The chemical structures of docetaxel and cabazitaxel are depicted below:

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[1] This publication is formally entitled "Approved Drug Products with Therapeutic Equivalence Evaluations."



Docetaxel



Cabazitaxel

As annotated above, cabazitaxel differs from docetaxel in the substitution of two methoxy groups for hydroxyl groups. The carbon atoms to which the right and left methoxy groups are bound are referred to as C7 and C10, respectively. A fully numbered cabazitaxel is depicted in Appendix A, and the carbon positions are numbered in the same way in docetaxel.[2]

Cabazitaxel was the product of a multi-year research program aimed at identifying taxane analogs with better activity than docetaxel in resistant tumors. By making substitutions at multiple positions on docetaxel with various functional groups, Sanofi scientists synthesized several hundred compounds and tested their activities. Of this group, cabazitaxel was one of two compounds that entered into human studies. It obtained FDA approval in 2010.

Fresenius and the other defendants-appellees[3] (collectively, "Defendants") filed Abbreviated New Drug Applications ("ANDAs") to market generic versions of cabazitaxel prior to the expiration of the '592 and '170 patents, prompting Sanofi to sue the Defendants for infringement in the District of New Jersey. Defendants counterclaimed for a

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[2] In contrast to docetaxel, paclitaxel, the other FDA-approved prior art taxane, has an acetoxy group at C10 instead of a hydroxyl. It also has a different sidechain group at C3′.

[3] Three defendants have not joined Fresenius's cross-appeal.

declaratory judgment of invalidity of the '592 patent. The case ultimately proceeded to a bench trial concerning both patents.

However, while the district court case was pending, the Patent Trial and Appeal Board (the "Board") of the United States Patent and Trademark Office instituted *inter partes* review of the '592 patent. Soon after the district court trial began, the Board held claims 1–5 and 7–30 unpatentable as obvious and denied Sanofi's motion to amend its claims. Although Sanofi did appeal from the Board's denial of its motion to amend, it did not appeal from the Board's decision with respect to claims 7, 11, 14–16, and 26. And on December 8, 2017, Sanofi filed a statutory disclaimer of those claims (the "disclaimed claims") in the Patent and Trademark Office and so informed the district court. J.A. 14135–36; *see* 37 C.F.R. § 1.321(a).

Soon after the disclaimer, the district court entered a post-trial order reaching two conclusions relevant to this appeal. First, despite the statutory disclaimer of the disclaimed claims, the court concluded that a case or controversy still existed with respect to those claims and that they were invalid as obvious. *Decision*, slip op. at 45–46, 79–83. Second, the court held that the Defendants failed to prove that claims 1 and 2 of the '170 patent, claiming the cabazitaxel compound and related pharmaceutical compositions (and set forth in Appendix B), would have been obvious over the prior art. *Id.* at 42–43.[4]

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[4] Over one year after the district court's judgment, and after the parties completed briefing in this appeal, we vacated the Board's decision denying Sanofi's motion to amend and remanded the case to the Board for further proceedings. *See Sanofi Mature IP v. Mylan Labs. Ltd.*, 757 F. App'x 988, 994 (Fed. Cir. 2019). We held that the Board erroneously placed the burden on Sanofi to prove the

Sanofi appealed from the district court's conclusion that a case or controversy still existed over the disclaimed claims after Sanofi's statutory disclaimer. Fresenius cross-appealed from the court's judgment of nonobviousness of claims 1 and 2 of the '170 patent. We have jurisdiction over both appeals under 28 U.S.C. § 1295(a)(1). We first address Sanofi's jurisdictional appeal and then turn to Fresenius's cross-appeal.

DISCUSSION

I

We review *de novo* whether a case or controversy existed for the district court to enter a declaratory judgment of noninfringement or invalidity, *Prasco, LLC v. Medicis Pharm. Corp.*, 537 F.3d 1329, 1335 (Fed. Cir. 2008), and apply Federal Circuit law, *3M Co. v. Avery Dennison Corp.*, 673 F.3d 1372, 1377 (Fed. Cir. 2012).

Sanofi argues that after it disclaimed the particular claims, there was no longer a case or controversy regarding those claims, and the district court thus lacked authority to invalidate them. Accordingly, Sanofi requests that we vacate the court's judgment invalidating the disclaimed claims.

Defendants respond that there may still have been a case or controversy over the disclaimed claims depending on the merits of their potential future issue or claim preclusion defense, which Defendants could raise if Sanofi succeeds in amending claims of the '592 patent and then

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patentability of the amended claims, and "decline[d] to speculate as to how the Board would resolve this case under the correct legal standard." *Id.* at 991. The case remains pending before the Board. *See Mylan Labs. Ltd. v. Aventis Pharma S.A.*, No. IPR2016-00712, 2019 WL 1559904 (P.T.A.B. Apr. 9, 2019), Paper No. 108.

asserts the amended claims against Defendants. That is, Defendants insist we must resolve this potential preclusion issue in the first instance in order to decide whether the district court had jurisdiction over the disclaimed claims.

Article III empowers federal courts to adjudicate only "Cases" and "Controversies," U.S. Const. art. III, § 2, "appropriately resolved through the judicial process," *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 560 (1992) (quoting *Whitmore v. Arkansas*, 495 U.S. 149, 155 (1990)). To satisfy the case or controversy requirement in the declaratory judgment context, the parties' dispute must be "'real and substantial' and 'admi[t] of specific relief through a decree of a conclusive character, as distinguished from an opinion advising what the law would be upon a hypothetical state of facts.'" *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007) (alteration in original) (quoting *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 240–41 (1937)). The case or controversy analysis is highly similar to that of Article III standing. *See Apotex, Inc. v. Daiichi Sankyo, Inc.*, 781 F.3d 1356, 1362 (Fed. Cir. 2015). "To have standing, a plaintiff must 'present an injury that is concrete, particularized, and actual or imminent; fairly traceable to the defendant's challenged behavior; and likely to be redressed by a favorable ruling.'" *Dep't of Commerce v. New York*, 139 S. Ct. 2551, 2565 (2019) (quoting *Davis v. Fed. Election Comm'n*, 554 U.S. 724, 733 (2008)). The injury must be "'concrete and particularized' and 'actual or imminent, not conjectural or hypothetical.'" *Spokeo, Inc. v. Robins*, 136 S. Ct. 1540, 1548 (2016) (quoting *Lujan*, 504 U.S. at 560).

Further, "an actual controversy *must be extant at all stages of review*, not merely at the time the complaint is filed." *Steffel v. Thompson*, 415 U.S. 452, 459 n.10 (1974) (emphasis added). We focus our analysis on whether there was an actual controversy when the district court entered final judgment. *See Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1362–63 & n.9 (Fed. Cir. 2008).

We agree with Sanofi that its disclaimer of the disclaimed claims mooted any controversy over them. As we explain, at the time the district court entered final judgment, the relief requested by Defendants was both speculative and immaterial to its possible future defenses, and Defendants thus failed to demonstrate an Article III case or controversy.

When Sanofi disclaimed the disclaimed claims, it "effectively eliminated those claims from the . . . patent," *Vectra Fitness, Inc. v. TNWK Corp.*, 162 F.3d 1379, 1383 (Fed. Cir. 1998), leaving the '592 patent "as though the disclaimed claim(s) had 'never existed,'" *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1299 (Fed. Cir. 2011) (quoting *Vectra*, 162 F.3d at 1383)). By leaving the '592 patent as if the disclaimed claims had never existed, Sanofi's disclaimer mooted any infringement-based dispute concerning those claims. *See Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 721 F.3d 1330, 1340 (Fed. Cir. 2013) ("[I]n general, when a claim is cancelled, the patentee loses any cause of action based on that claim, and any pending litigation in which the claims are asserted becomes moot.").

Nonetheless, Defendants contend that the district court's invalidity judgment with respect to the disclaimed claims must be preserved to provide them with "patent certainty," relying principally on our decision in *Teva Pharmaceuticals USA, Inc. v. Novartis Pharmaceuticals Corp.*, 482 F.3d 1330 (Fed. Cir. 2007). In that case, Teva brought a declaratory judgment action against four Orange Book-listed patents owned by Novartis. *Id.* at 1335. We concluded that there was a case or controversy sufficient for declaratory judgment jurisdiction concerning those patents because Teva had submitted an ANDA certifying that the patents were invalid or not infringed, and Novartis had already sued Teva on another listed patent covering the same product. *Id.* at 1340–44. The controversy in *Teva* thus related to a concrete and realistic threat posed by existing

patent claims. Defendants point to no such threat created by the effectively nonexistent disclaimed claims, so Defendants' reliance on *Teva* is misplaced.

In some circumstances, patent claims may create a controversy sufficient for declaratory judgment jurisdiction even when there is no risk of infringement, but the party seeking such judicial relief must demonstrate some other concrete and imminent harm traceable to the claims. *See Daiichi Sankyo*, 781 F.3d at 1361–62; *see also Amerigen Pharm. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1083–84 (Fed. Cir. 2019). Defendants have not done so in this case.

Defendants allege that if we vacate the district court's judgment of invalidity of the disclaimed claims, then Defendants will lose the possible benefit of an issue preclusion defense based on that judgment should Sanofi obtain amended claims and assert them against Defendants. We conclude that this alleged injury did not provide a case or controversy at the time of the court's judgment for at least two reasons.

First, the relevance of the disclaimed claims to a possible issue preclusion defense was speculative. An Article III court may not "advis[e] what the law would be upon a hypothetical state of facts." *MedImmune*, 549 U.S. at 127 (internal quotation marks omitted). When the district court issued its decision, there were no enforceable amended claims. The Board had denied Sanofi's motion to amend, so any future assertion of amended claims was premised on a hypothetical appellate reversal or vacatur and remand of the Board's *inter partes* review decision.

Second, even assuming that Defendants' stake in the district court's judgment concerning the disclaimed claims was sufficiently imminent, they have not established that the judgment pertaining to those claims is material to a possible future suit. Defendants contend that they have an interest in preserving, for possible issue preclusion

purposes, the court's purported finding "[i]n connection with disclaimed claim 11" that "dosages of cabazitaxel beyond 20 mg/m^2 were in the prior art and used to treat docetaxel-resistant prostate cancer." Cross-Appellants' Br. 47–48. They cite two sections of the court's decision as relevant to that finding. However, the first section addresses only claims 21 and 30, not disclaimed claim 11, and thus would be entirely unaffected by vacatur of the court's decision regarding the disclaimed claims. *See Decision*, slip op. at 75 (discussing claims 21 and 30 and finding that "[t]he TROPIC trial was a trial done at a dose of 25 mg/m^2 of cabazitaxel"). And while the second section does discuss claim 11, it does not examine dosages above 20 mg/m^2. Defendants have thus failed to demonstrate that vacatur of the court's judgment regarding the disclaimed claims would matter to its potential issue preclusion argument.

Somewhat relatedly, Defendants ask us to consider in the first instance the claim preclusion arguments that they intend to make—based on Sanofi's previous assertion of certain non-disclaimed claims—should Sanofi secure amended claims at the Board and then assert them against Defendants. Defendants do not allege, however, that this hypothetical defense in any way depends on the district court's judgment concerning the disclaimed claims. We cannot issue an advisory opinion on such a theoretical dispute and we decline to do so here. Defendants will have ample opportunity to raise a claim preclusion defense at the district court should Sanofi sue them again.

For these reasons, Defendants have not shown the existence of a case or controversy over the disclaimed claims at the time the district court entered judgment. The court thus lacked authority to disinter the already disclaimed claims and declare them invalid. Accordingly, we vacate the court's judgment concerning the disclaimed claims.

II

We now turn to Fresenius's cross-appeal from the district court's judgment that cabazitaxel, claimed in claims 1 and 2 of the '170 patent, would not have been obvious over docetaxel, which has been determined to be the lead compound and, in effect here, the closest prior art. On appeal from a bench trial, we review a district court's conclusions of law *de novo* and its findings of fact for clear error. *Braintree Labs., Inc. v. Novel Labs., Inc.*, 749 F.3d 1349, 1358 (Fed. Cir. 2014). A factual finding is clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948). "The burden of overcoming the district court's factual findings is, as it should be, a heavy one." *Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1559 (Fed. Cir. 1986). A patent is presumed valid, and overcoming that presumption at the district court requires clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011); *Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1401, 1407 (Fed. Cir. 2014).

Obviousness is a question of law based on underlying facts, including the scope and content of the prior art, differences between the prior art and the claims at issue, the level of ordinary skill, and relevant evidence of secondary considerations. *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17–18 (1966). "[I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). The reason need not be the same as the patentee's or expressly stated in the art. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007); *see In re Dillon*, 919 F.2d 688, 693–94 (Fed. Cir. 1990) (en banc). But charting a path to the claimed compound by hindsight is not enough to prove

obviousness. "Any compound may look obvious once someone has made it and found it to be useful, but working backwards from that compound, with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen*, 913 F.3d at 1089.

In its obviousness analysis, the district court considered the testimony of seven witnesses and seventeen prior art references and ultimately concluded that Defendants failed to prove that claims 1 and 2 of the '170 patent would have been obvious. *Decision*, slip op. at 43. The court found that a person of ordinary skill would have selected docetaxel as a lead compound, and the key issue was thus whether a skilled artisan would have been motivated to replace the C7 and C10 hydroxyl groups of docetaxel with the methoxy groups of cabazitaxel. *Id.* at 30. We summarize the court's extensive findings on this issue as pertinent to this appeal.

Defendants argued at the district court that a skilled artisan would have been motivated to increase the lipophilicity of docetaxel to interfere with a protein called Pgp and thereby thwart drug resistance. Generally, the district court credited undisputed expert testimony that Pgp was involved in one of several possible mechanisms for drug resistance. *Id.* at 36. Functioning as a protein pump, Pgp can remove drug compounds from a cell and thereby hinder their therapeutic effect. The court made findings

concerning two references relating to Pgp, Hait[5] and Lampidis,[6] which we review here.

Hait discussed how Pgp could contribute to multi-drug resistance and proposed a binding model for Pgp inhibitors. J.A. 25093–94. The reference studied a group of Pgp inhibitors called phenothiazines, which have a tricyclic ring structure quite different from taxanes, and found that increasing lipophilicity increased sensitivity of a cancer cell line to a non-taxane therapeutic. J.A. 25093. The district court found that Hait would not have motivated a skilled artisan to modify docetaxel for several reasons. The court found that Hait addressed the effect of phenothiazines, not taxanes, on Pgp, and that phenothiazines were structurally quite different from taxanes. *Decision*, slip op. at 34. Consistent with that fact, the court observed that no prior art taxane reference of record cited Hait. *Id.* Additionally, the court found that Hait only presented a hypothetical model of Pgp binding based on the binding site of a different protein. *Id.*

The district court found similarly with respect to Lampidis. Lampidis reported that increasing the lipophilicity of a positively-charged dye beneficially increased accumulation of the dye in drug resistant cells. J.A. 16954. As with Hait, however, the district court found that Lampidis never discussed taxanes. *Decision*, slip op. at 34. Further, the court determined that the reference focused on increasing the lipophilicity of positively-charged compounds, but taxanes do not have a positive charge. *Id.*; *see* Lampidis,

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[5] William N. Hait & Dana T. Aftab, *Rational Design and Pre-Clinical Pharmacology of Drugs for Reversing Multidrug Resistance*, 43 Biochemical Pharmacology 103 (1992).

[6] Theodore J. Lampidis et al., *Relevance of the Chemical Charge of Rhodamine Dyes to Multiple Drug Resistance*, 38 Biochemical Pharmacology 4267 (1989).

J.A. 16954 ("If our hypothesis is correct, then it would appear that, in general, as we increase the lipophilicity of *positively charged* (delocalized) *compounds* we increase their abilities to accumulate in, and subsequently kill, MDR cells." (emphasis added)).

The district court also considered the teachings of two articles that identified possible positions for substitution on taxanes. Commerçon[7] identified the C3′, C7, C9, and C10 positions on paclitaxel as "flexible" and suitable for modification and also identified C2′ as a possible site for certain modifications if the configuration of the group is maintained. J.A. 25161. Kingston 1994[8] was similar.

In addition to these articles, the district court addressed numerous references that investigated the activity of specific taxane analogs. We review these here.

European Patent Application 0 639 577 ("Golik") substituted a methylthiomethoxy group for the C7 hydroxyl of paclitaxel and reported that the compound had increased activity *in vitro* compared to docetaxel and paclitaxel in a drug-resistant cell line. J.A. 25205–06, 25229; *Decision*, slip op. at 23. Golik also modified the C2′ position with a prodrug moiety, and this analog showed promising results *in vivo*. J.A. 25208, 25261; *Decision*, slip op. at 30. The court found no evidence that Golik's methylthiomethoxy substitution at C7 would lead a skilled artisan to make a

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[7] A. Commerçon et al., *Practical Semisynthesis and Antimitotic Activity of Docetaxel and Side-Chain Analogues*, *in* Taxane Anticancer Agents: Basic Science and Current Status 233 (G. I. Georg et al. eds., 1994).

[8] David G. I. Kingston, *Recent Advances in the Chemistry and Structure-Activity Relationships of Paclitaxel*, *in* Taxane Anticancer Agents: Basic Science and Current Status 206 (G. I. Georg et al. eds., 1994).

methoxy substitution at that position. *Decision*, slip op. at 31.

The other reference studying the activity of taxane analogs against drug-resistant cell lines was Ojima 1994.[9] Ojima 1994 reported that modifying C3′ with certain substitutions produced much better activity than paclitaxel and docetaxel against a drug-resistant cell line. J.A. 25114–15. The reference disclosed neither a C7 nor a C10 methoxy substitution. The court found that Ojima 1994 did not teach increasing lipophilicity of C7 and C10 against drug resistant cells. *Decision*, slip op. at 34–35.

U.S. Patent 6,201,140 ("Wong") disclosed a paclitaxel derivative with a methoxy substitution at C7. J.A. 25324. However, the district court found that Wong disclosed a more potent paclitaxel derivative with a C2′ modification and a different ether substitution at C7. *Decision*, slip op. at 31. Further, the court found that Wong did not disclose any compound with the C10 hydroxyl of docetaxel or the C10 methoxy of cabazitaxel and did not disclose activity data from resistant cell lines. *Id.*

Another reference considered by the district court, Kant,[10] focused on substitutions at C10, including a C10 methoxy substitution. Kant did not evaluate the activity of C10 analogs in drug resistant cell lines and compared the C10-methoxy-substituted docetaxel only to paclitaxel, not docetaxel. J.A. 25311–12. Kant also did not study any

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[9] Iwao Ojima et al., *Syntheses and Structure-Activity Relationships of New Taxoids*, *in* Taxane Anticancer Agents: Basic Science and Current Status 262 (G. I. Georg et al. eds., 1994).

[10] Joydeep Kant et al., *A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III. Synthesis and Biological Properties of Novel C-10 Taxol® Analogues*, 35 Tetrahedron Letters 5543 (1994).

C7 substitutions. Although the court observed that the C10 methoxy substitution (along with another analog) showed good results in one assay, another compound performed better in a different assay. *Decision*, slip op. at 32.

The district court proceeded to Klein,[11] which focused on substitutions at C9. Klein reported that certain C9-substituted taxanes "have increased water solubility and stability as compared to [paclitaxel] and also exhibit excellent activity in tumor models." J.A. 25173. Klein also disclosed simultaneous C7 and C9 substitutions, including a C7 methoxy with good activity, but no C10 substitutions. J.A. 25178. As with Wong and Kant, the court observed that Klein did not investigate the activity of these substituted taxanes on drug resistant cell lines. *Decision*, slip op. at 33.

Ultimately, the district court found Defendants' experts cherry-picked data in the references to reach cabazitaxel and were not credible. *Id.* at 36. The court credited Sanofi's expert's testimony that taxane modifications were considered at C2, C4, C5, C7, C8, C9, C10, C11, C12, C13, C14, C2′, and C3′, *id.* at 37, and concluded that it would not have been obvious to make simultaneous methoxy substitutions at C7 and C10 of docetaxel, *id.*

In addition, the district court found that some secondary considerations evidence supported nonobviousness and that there was a nexus between claims 1 and 2 and the marketed product Jevtana®. *Id.* at 37–38. Despite attempts by research groups around the world to develop effective taxane cancer treatments, the court recognized that cabazitaxel was only the third taxane to obtain FDA

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[11] L. L. Klein et al., *Chemistry and Antitumor Activity in 9(*R*)-Dihydrotaxanes*, *in* Taxane Anticancer Agents: Basic Science and Current Status 276 (G. I. Georg et al. eds., 1994).

approval. *Id.* at 40–41. The court thus determined that "[Sanofi's] success, where others had failed," supported nonobviousness. *Id.* at 41. The court also found that Jevtana® achieved commercial success. *Id.* at 42. In light of all the evidence, the court concluded that Defendants failed to prove obviousness by clear and convincing evidence. *Id.* at 43.

In its cross-appeal, Fresenius argues that the district court committed a "cascading series of factual and legal errors." Cross-Appellants' Br. 67. Specifically, Fresenius alleges that the court erred in rejecting its theory that a skilled artisan would have: (1) been motivated to modify docetaxel to reduce Pgp-related drug resistance; (2) knew that this could be accomplished by increasing lipophilicity of the C7 and C10 positions; and (3) determined that methoxy substitutions were the "smallest, most conservative" modification to achieve that goal. *Id.* Fresenius further argues that the evidence of secondary considerations does not overcome the evidence of obviousness.

Sanofi responds that Fresenius's obviousness theory was hindsight-driven and that the district court did not err in rejecting it.

We agree with Sanofi and conclude that Fresenius's convoluted obviousness theory lacks merit. We begin with Fresenius's contention that the district court clearly erred in finding that Hait and Lampidis would not have provided a reason to make docetaxel more lipophilic. Not only did these references not contemplate taxanes, they investigated compounds that are structurally very different from taxanes. Lampidis focused on positively-charged dyes and suggested that increasing lipophilicity of positively-charged molecules could be beneficial, but docetaxel is not positively charged. Likewise, Hait studied phenothiazines, which are much smaller than taxanes and have a three-ring structure bearing no resemblance to taxanes. Furthermore, Hait only presented a hypothetical binding site

model based on a different protein than Pgp. And the evidence showed that no prior art taxane reference cited Hait. *Decision*, slip op. at 34. We conclude that the court did not clearly err in its assessment of these references or in finding that they would not have motivated a skilled artisan to modify docetaxel to obtain cabazitaxel.

Even assuming there was some general motivation to make docetaxel more lipophilic to combat drug resistance, the district court also did not clearly err in finding that Fresenius failed to establish a motivation to do so by specifically making simultaneous methoxy substitutions at C7 and C10. The court found that taxane researchers investigated substitutions at many positions, and the voluminous references in this case support that finding. For example, Commerçon disclosed that C3′, C7, C9, and C10, and to a more limited extent C2′, were modifiable. And as summarized above, the other references investigated a diverse set of substitutions. Fresenius reads this panoply of teachings as rendering obvious simultaneous C7 and C10 methoxy substitutions. But despite the apparent interest in taxane analogs, not a single reference relied on by Fresenius made simultaneous substitutions of any kind at C7 and C10. And of the references that made individual methoxy substitutions at C7 or C10, none tested those taxane analogs against drug resistant cell lines or taught that the analogs would overcome drug resistance. On this record, the court did not clearly err in finding no motivation to make C7 and C10 methoxy substitutions on docetaxel to improve its activity against drug-resistant cancers.

Considering Fresenius's reference-specific arguments, we agree with the district court that they are emblematic of hindsight reasoning. Fresenius contends that Commerçon would have pointed a skilled artisan towards C7, C10, and (less desirably) C9 substitutions because those positions were "flexible," and away from C2′ and C3′ substitutions because those positions were "crucial." Cross-Appellants' Br. 57–58. However, this argument plainly

mischaracterizes the reference. Commerçon expressly identified the sidechain position C3′ as "flexible," and indicated that C2′ could be modified with certain substitutions if the configuration was maintained. J.A. 25161–62.

That teaching is consistent with references such as Ojima 1994 that investigated sidechain substitutions on taxanes. *See* Ojima 1994, J.A. 25104 (C3′ substitutions); Wong, J.A. 25327 (C2′ substitution). Fresenius, however, contends that Ojima 1994 would motivate a skilled artisan to make a C10 methoxy substitution because it showed that "changing a hydrophilic hydroxy group to a more lipophilic methoxy group at C-10 resulted in a significant increase in potency against drug resistant cells." Cross-Appellants' Br. 62. As with its argument concerning Commerçon, Fresenius's position is premised on an incorrect characterization of the reference. The portions of Ojima 1994 in the record nowhere investigated a methoxy-substituted taxane, at C10 or anywhere else. While two of the compounds tested did have paclitaxel's C10 acetoxy group, Ojima 1994 did not even mention that fact. Rather, it emphasized the "excellent" or "noteworthy" activity associated with C3′ isobutyl and isobutenyl substitutions. J.A. 25114–15. We conclude that the district court did not clearly err in rejecting Fresenius's selective reading of the reference.

Although no cited reference shows that C7 or C10 methoxy-substituted taxanes have improved properties with respect to drug resistance, Fresenius argues that a skilled artisan would have made simultaneous C7 and C10 methoxy substitutions because they are "small, conservative changes" that increase lipophilicity. Cross-Appellants' Br. 65–67 (citing *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 974–75 (Fed. Cir. 2014)). Fresenius's arguments concerning Golik are illustrative. As previously discussed, Golik disclosed a taxane analog with a methylthiomethoxy substitution at C7, which had promising qualities against drug-resistant cell lines. Rather than simply motivate a skilled artisan to investigate C7

methylthiomethoxy substitutions, Fresenius argues that this teaching really supports making a C7 *methoxy* substitution.

This argument stands on little more than hindsight. The district court found no evidence that the methoxy group would provide a similar benefit as the sulfur-containing methylthiomethoxy group. *Decision*, slip op. at 30–31. In contrast to the reported advantageous features of the methylthiomethoxy group in Golik and the absence of any evidence showing equivalent properties of a methoxy substitution, Fresenius directs us on appeal only to its experts' vague testimony that sulfur has some unspecified "metabolic liabilities" or "other complications." J.A. 12361–62, 13160. We conclude that the court did not clearly err in rejecting this weak testimony.

Fresenius's position concerning Ojima 1994 is similar. Fresenius argues that Ojima 1994's supposed implicit teaching of the benefits of a C10 *acetoxy* group against drug-resistant cells would actually motivate a skilled artisan to make a C10 *methoxy* substitution because it is smaller and more conservative. As with Golik, Fresenius cites no non-conclusory evidence that the methoxy group would have the same purported benefits as the acetoxy group, and offers no persuasive explanation of how the methoxy group, which was not tested in Ojima 1994, would be a more conservative choice than the C10 acetoxy already present in the FDA-approved drug paclitaxel. We consider Fresenius's argument exemplary of hindsight reasoning.

Many of Fresenius's arguments cite our decision in *Bristol-Myers Squibb*. There, we affirmed a district court's conclusion that it would have been obvious to make a single chemical change to a lead compound where there were a "small, finite number of changes to try," and the particular claimed change had already been shown to have desirable properties in a similar context. *Bristol-Myers Squibb Co.*, 752 F.3d at 975–76 (quoting *In re Cyclobenzaprine*

Hydrochloride Patent Litig., 676 F.3d 1063, 1072 (Fed. Cir. 2012)). As our review above shows, the district court's findings in this case are quite different and demand a different outcome. The court here found that numerous docetaxel modifications were under investigation, and there was no showing that making individual or simultaneous methoxy substitutions at C7 and C10 improved activity against drug-resistant cells, the sole motivation relied on by Fresenius. We also disagree with Fresenius that small changes to a compound are necessarily *prima facie* obvious. We did not adopt such a bright-line legal rule in *Bristol-Myers Squibb*, and doing so would be inconsistent with the flexible analysis inherent to the highly contextual obviousness inquiry. *See KSR*, 550 U.S. at 415.

Fresenius last challenges the district court's weighing of the evidence of secondary considerations, although it does not point to any error in the court's reasoning. We see no clear error in the court's finding that "[m]ultiple groups around the world tried unsuccessfully to develop taxanes into effective therapies and only [Sanofi] succeeded in developing a compound that showed superior activity over docetaxel, namely cabazitaxel, and obtained FDA approval." *Decision*, slip op. at 41 (citations omitted). And we agree with the court that, in this case, this finding warrants significant weight in the ultimate obviousness analysis. We also conclude that the court did not clearly err with respect to Sanofi's evidence of commercial success.

Ultimately, we agree with Sanofi that the district court correctly concluded that claims 1 and 2 of the '170 patent would not have been obvious over docetaxel. We have also considered Fresenius's other arguments but find them unpersuasive. We thus affirm the court's judgment.

CONCLUSION

For the foregoing reasons, we vacate the district court's judgment of obviousness concerning claims 7, 11, 14–16, and 26 of the '592 patent and affirm the court's judgment

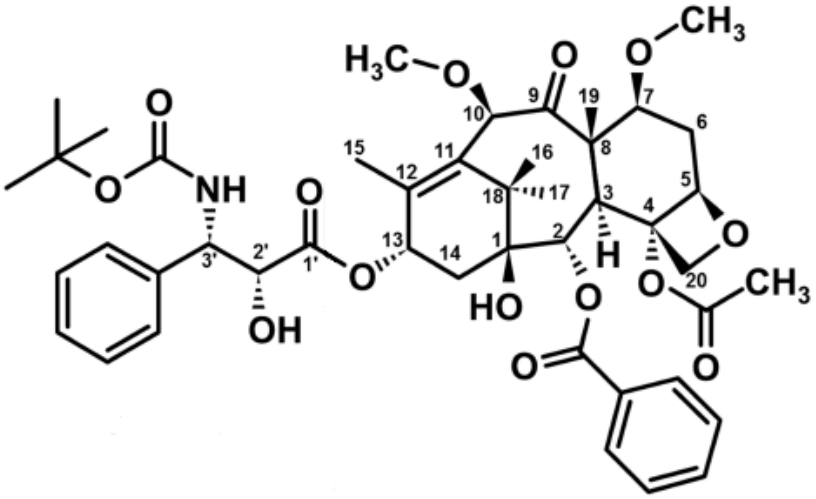
of nonobviousness concerning claims 1 and 2 of the '170 patent.

AFFIRMED-IN-PART AND VACATED-IN-PART

COSTS

Costs to Sanofi.

APPENDIX A



Cabazitaxel

APPENDIX B

'170 Patent Claim 1

> 1. 4α-Acetoxy-2α-benzoyloxy-5ß,20-epoxy-1ß-hydroxy-7ß,10ß-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

'170 Patent Claim 2

> 2. A pharmaceutical composition comprising at least the product according to claim 1 in combination with one or more pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds.