NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

TRIS PHARMA, INC.,
Plaintiff-Appellee

v.

ACTAVIS LABORATORIES FL, INC.,
Defendant-Appellant

2021-1495

Appeal from the United States District Court for the District of Delaware in Nos. 1:14-cv-01309-CFC, 1:15-cv-00393-CFC, 1:15-cv-00969-CFC, Judge Colm F. Connolly.

Decided: July 7, 2022

ERROL TAYLOR, Milbank LLP, New York, NY, argued for plaintiff-appellee. Also represented by JORDAN BENJAMIN FERNANDES; MONICA ARNOLD, LAUREN NICOLE DRAKE, Los Angeles, CA.

BRIAN TIMOTHY BURGESS, Goodwin Procter LLP, Washington, DC, argued for defendant-appellant. Also represented by JORDAN BOCK, Boston, MA; ALEXANDRA D. VALENTI, New York, NY; ELIZABETH HOLLAND, Allen &

Overy LLP, New York, NY; WILLIAM G. JAMES, II, Washington, DC.

Before MOORE, *Chief Judge*, CHEN and HUGHES, *Circuit Judges*.

CHEN, *Circuit Judge*.

Appellant Tris Pharma, Inc. (Tris) owns U.S. Patent Nos. 8,465,765 ('765 patent), 8,563,033 ('033 patent), and 8,778,390 ('390 patent). Tris asserted claims of all three patents against Appellee Actavis Laboratories FL, Inc. (Actavis) in the United States District Court for the District of Delaware. Following a five-day bench trial, the district court held that all asserted claims would have been obvious under 35 U.S.C. § 103. *Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, 276 F. Supp. 3d 226, 249 (D. Del. 2017). In September 2017, Tris appealed the district court's decision to this court. We held that the district court "failed to make the necessary factual findings and provide sufficient analysis of the parties' arguments to permit effective appellate review." *Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, 755 F. App'x 983, 989 (Fed. Cir. 2018) (*Tris I*). Accordingly, we vacated and remanded for further fact-finding.[1] *Id.* at 993. On remand, the district court considered the trial record,

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[1] On appeal, Tris argues that our 2018 vacatur preserved certain fact-findings made by the district court. Appellant's Br. 34–36. For the avoidance of doubt, our 2018 decision vacated the district court's decision in its entirety and "invite[d] the district court to reconsider all the evidence of objective indicia in its overall determination of obviousness." *Tris I* at 984, 993; *see also State Indus., Inc. v. Mor-Flo Indus., Inc.*, 948 F.2d 1573, 1577 (Fed. Cir. 1991) (finding that a district court's findings could not constitute law of the case where the court's decision was vacated and the court was instructed to reconsider).

post-trial record, and the parties' post-remand briefing. *Tris Pharma, Inc. v. Actavis Lab'ys FL, Inc.*, 503 F. Supp. 3d 183, 185 (D. Del. 2020) (*Remand Decision*). Based on its review, the district court concluded that Actavis failed to prove by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to combine the prior art references with a reasonable expectation of success. *Id.* at 202–03. Accordingly, the district court held that Actavis failed to show that the challenged claims[2] would have been obvious. *Id.* This appeal followed. Because the district court's conclusions are not clearly erroneous, we *affirm*.

I

A

The asserted claims relate to a liquid methylphenidate (MPH) oral suspension with certain pharmacodynamic and pharmacokinetic properties. '765 patent col. 1 ll. 52–55; '033 patent col. 1 ll. 58–61; '390 patent col. 1 ll. 63–66. MPH is an active ingredient in several pharmaceutical formulations used to treat, *inter alia*, attention deficit hyperactivity disorder. *See, e.g.*, '033 patent col. 21 ll. 17–29. Claim 10 of the '033 patent, which depends from claims 1 and 9, is exemplary:

> 1. A methylphenidate aqueous extended release oral suspension comprising (1) an immediate release methylphenidate component, (2) a sustained release methylphenidate component, and (3) water, said suspension having a pH of about 3.5 to about 5,

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[2] The claims at issue on remand and in this appeal are claims 6 and 20 of the '765 patent, claims 4 and 10 of the '033 patent, and claims 15, 16, and 20 of the '390 patent. *Remand Decision* at 185; *see also* Appellant's Br. 6.

> wherein said suspension provides a single mean average plasma concentration peak and a therapeutically effective plasma profile for about 12 hours for methylphenidate, and
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> wherein the suspension has a pharmacokinetic profile in which the single mean plasma concentration peak for methylphenidate has an area under the curve $(AUC)_{0\rightarrow\infty}$ of about 114 to about 180 ng-hr/mL, C_{max} of about 11 to about 17 ng/mL, T_{max} of about 4 to about 5.25 hours, and $T_{1/2}$ of about 5 to about 7 hours following a single oral administration of said suspension at a dose equivalent to 60 mg racemic methylphenidate HCl in adults.
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> * * *
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> 9. A method for treating a patient having a condition susceptible to treatment with methylphenidate, the method comprising administering to the patient the suspension according to claim 1, wherein said suspension provides a therapeutically effective amount of methylphenidate within 45 minutes after administering of said suspension and a single average plasma concentration peak.
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> 10. The method according to claim 9, wherein the suspension which has a pH from about 4 to about 4.5.

The limitations relevant to the district court's remand determinations and this appeal are "aqueous," "therapeutically effective plasma profile . . . for about 12 hours" (12-hour duration), "therapeutically effective amount of methylphenidate within 45 minutes" (45-minute onset), "T_{max} of about 4 to about 5.25 hours" (early T_{max} range), and "single mean plasma concentration peak" (single mean peak). Aside from "aqueous," these properties describe the change in concentration of MPH in the patient's

bloodstream over time. A 12-hour duration indicates that the formulation has an "extended release" whereby it achieves clinical effects for about 12 hours. '033 patent col. 4 ll. 15–24, col. 17 ll. 34–39, col. 22 ll. 4–6, col. 37 ll. 28–31. A 45-minute onset indicates that the formulation reaches therapeutically effective levels of MPH within 45 minutes of administration. *Id.* col. 4 ll. 21–23, col. 5 ll. 5–8, col. 21 ll. 39–42, col. 25 ll. 22–25. Following administration, the concentration of MPH in the patient's bloodstream will vary due to chemical and biological processes and will eventually reach a maximum. A T_{max} of about 4 to about 5.25 hours indicates that the maximum concentration occurs about 4 to 5.25 hours after administration. *Id.* col. 4 ll. 43–45, col. 19 ll. 22–31, col. 36 l. 31. The single mean peak limitation describes the shape of the concentration curve, conveying that the concentration over time has only one maximum. *See, e.g.*, *id.* FIG. 3.

All of the claims at issue require a liquid MPH formulation with a 12-hour duration and single mean peak. Claim 20 of the '765 patent additionally requires a 45-minute onset, while claim 6 of the '765 patent, claim 4 of the '033 patent, and claims 15, 16, and 20 of the '390 patent require the early T_{max} range. Only claim 10 of the '033 patent, set forth above, encompasses all of these features.

B

Both in the original district court proceeding and on remand, Actavis relied on five commercially available MPH formulations (Concerta®, Daytrana®, Focalin XR®, Metadate CD®, and Ritalin LA®), U.S. Patent Application Publication No. 2010/0260844 (Scicinski), and several scientific articles as prior art. *Remand Decision* at 191; *see also Tris I* at 985. The references disclose various subsets of the claim limitations, but no single reference discloses all of the limitations in any given claim. *Remand Decision* at 195. For example, the district court found that Concerta® has a 12-hour duration and a T_{max} that overlaps with the claimed

T_{max} range. *Id.* at 191. However, Concerta® is a tablet (not liquid) with a bimodal (not single) mean peak and an onset time greater than 45 minutes. *Id.* at 191–93. Similarly, the district court found that the hypothetical formulation described in Scicinski discloses a 12-hour duration, a single mean peak, and a T_{max} within the claimed range but does not disclose a 45-minute onset or a liquid formulation. *Id.* at 193–95.

C

On remand, the district court found that Actavis failed to demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine prior art references disclosing certain subsets of the claimed features with a reasonable expectation of success. *Id.* at 203.

For claim 20 of the '765 patent, which claims a 45-minute onset but not the early T_{max} range, the district court found that Actavis failed to prove by clear and convincing evidence that "an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success a liquid MPH formulation with a single mean peak, 12-hour duration, and 45-minute onset." *Remand Decision* at 202. In particular, the district court found that Actavis did not present evidence demonstrating that a skilled artisan would have pursued a single mean peak concentration profile. *Id.* at 196–200, 202–03. Instead, Actavis only showed that single or bimodal peaks were potential options and the prior art taught away from using a single mean peak. *Id.* at 196–200, 202–03. The district court also found that the evidence the parties presented regarding objective indicia of nonobviousness supported that conclusion. That evidence indicated that a liquid formulation with the claimed pharmacokinetic and pharmacodynamic properties was "an unexpected result," particularly in light of evidence that there was a "long-felt unmet need" for such a formulation. *Id.* at 200–01.

For claim 6 of the '765 patent, claim 4 of the '033 patent, and claims 15, 16, and 20 of the '390 patent, all of which claim the early T_{max} range but not the 45-minute onset, the district court found that Actavis failed to show that "an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success a liquid MPH formulation with a single mean peak, 12-hour duration, and the claimed T_{max} range." *Remand Decision* at 203. For this group of claims, Actavis relied on only Scicinski to argue that the claims are invalid as obvious. *Id.* The district court found that while Scicinski discloses "the single mean peak, 12-hour duration, and claimed T*max* range . . . [t]he asserted claims require that the invention be a liquid formulation of MPH." *Id.* Specifically, the district court found that Actavis failed to demonstrate that Scicinski teaches a liquid formulation with the desired characteristics or that Scicinski provides any data or explanation as to why a liquid formulation could achieve the desired pharmacokinetic or pharmacodynamic properties. *Id.* at 201–02.

Because claim 10 of the '033 patent requires both the 45-minute onset and early T_{max} range, the district court found that Actavis failed to demonstrate a motivation to combine with a reasonable expectation of success for the same reasons. *Id.* at 202, 203. Accordingly, the district court held that all of the asserted claims would not have been obvious. Actavis appealed and we have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II

A

Obviousness is a mixed question of law and fact. We review the district court's legal conclusions regarding obviousness de novo and any factual findings for clear error. *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 728 (Fed. Cir. 2017). Whether there is a motivation to combine with a reasonable expectation of success is one such

factual issue. *Id.* (citing *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000)). Whether objective indicia support a finding of nonobviousness is another. *Id.* (citing *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 833 (Fed. Cir. 2015)). A factual finding is clearly erroneous only if "despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made." *Merck*, 874 F.3d at 728.

B

On appeal, Actavis argues that the district court erred in finding no motivation to combine with a reasonable expectation of success. However, the district court's findings are supported by the record and Actavis has failed to show any clear error by the district court. On remand, the district court considered and weighed the evidence presented in the parties' post-remand briefing, post-trial briefing, the trial record, and the pretrial order. *Remand Decision* at 185. In light of that record, the district court engaged in the further fact-finding requested by this court regarding whether the prior art rendered the challenged claims obvious and ultimately concluded Actavis had not met its burden regarding motivation to combine or reasonable expectation of success. *Id.* at 202–03; *see also Tris I* at 990 & n.5 (explaining that "Actavis needs to demonstrate that a skilled artisan would have been motivated to create a liquid formulation of MPH" that "use[s] a single mean peak [pharmacokinetic] profile to achieve a formulation with a 45-minute onset of action and/or a 12-hour duration of effect with a reasonable expectation of success").

1. 45-Minute Onset Claims

For claim 20 of the '765 patent, requiring a 45-minute onset but not a particular T_{max}, Actavis argued, without supporting evidence, only that a skilled artisan would have been generally motivated to use a single mean peak concentration profile. *Remand Decision* at 196. The district court found that, even accepting Actavis's argument, this

was insufficient to show that a skilled artisan would have been motivated to combine a single mean peak profile with "a liquid formulation with a 12-hour duration and 45-minute onset" to achieve the claimed invention. *Id.*; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (explaining that there must be "a reason" for a skilled artisan "to combine the elements in the way the claimed new invention does"). Additionally, the district court reasonably found, the only evidence presented by Actavis regarding motivation to combine was, at best, inconsistent. *Remand Decision* at 196–97. For example, Actavis presented expert testimony that a skilled artisan "would have been indifferent" to and therefore *not* motivated to use a single peak profile. *Id.* at 197–98; *see also id.* at 197 ("[A]ccording to Actavis, its own expert established at trial that an artisan of ordinary skill would have been indifferent (i.e., would have lacked motivation) to use a formulation that produced a single peak profile."); Appellant's Br. 39 ("Expert testimony established that a skilled artisan would not have been concerned about the shape of the plasma curve[.]"). The same expert also testified that a single peak profile did not necessarily correlate with clinical effects, such as the claimed 12-hour duration or 45-minute onset. *Remand Decision* at 197. Similarly, one of the inventors testified that there was no perceived benefit to having a single peak profile. *Id.* at 198. If anything, the district court concluded, this evidence is inconsistent with a motivation to combine the prior art references with a reasonable expectation of success. We see no error.

In fact, the district court reasonably found that the prior art taught away from pursuing a liquid formulation with a single peak, 12-hour duration, and 45-minute onset. *Id.* at 200. For example, the district court credited testimony that early MPH formulations with single mean peak profiles were considered "'robust failure[s]' because of their inability to produce an early onset and extended duration effect." *Id.* at 199. The district court also considered expert

trial testimony that a single mean peak, 12-hour duration, and 45-minute onset were incompatible characteristics. *Id.* at 199–200. With a finite dosage of MPH, a formulator chooses between a medication with an early single mean peak and fast onset that will be metabolized quickly, and a medication that is absorbed slowly with a single mean peak later in time. *Id.* at 199–200. "So use of the single mean peak profile therefore can quickly achieve a 45-minute onset but not a 12[-]hour effect, or can achieve a 12[-]hour effect but not an earlier onset." *Id.* at 200. To achieve both an early onset and longer duration, a formulator would seek a concentration profile with two separate (bimodal) peaks. *Id.* Contrary to Actavis's assertion that a formulation that produces a single mean peak profile would have been obvious to try, Appellant's Br. 39–40, this evidence supports the district court's conclusion that Actavis failed to show a skilled artisan would have been motivated to combine prior art references with these competing features to yield a single mean peak profile and that a skilled artisan would have a reasonable expectation of success in pursuing such an option. *See Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020) (affirming a district court's finding of no motivation to combine where the district court "properly weighed the evidence presented and concluded as a matter of fact that a [skilled artisan] would be dissuaded from selecting or combining the components as claimed"); *see also Rembrandt Wireless Techs., LP v. Samsung Elecs. Co.*, 853 F.3d 1370, 1379 (Fed. Cir. 2017).

On appeal, Actavis also challenges the district court's decision based on its purported failure to fully consider the disclosures in Scicinski. Appellant's Br. 38–39. Actavis argues that "[b]ecause Scicinski showed that early onset could be achieved with a single mean peak and extended duration, a skilled artisan would have been motivated to keep those features while accelerating onset to the stipulated 45-minute goal." *Id.* at 39; *see also id.* at 42. But, as the district court found, Scicinski taught neither a liquid

formulation nor a 45-minute onset. *Remand Decision* at 193–94. Scicinski would therefore need to be adapted to achieve the desired pharmacokinetic and pharmacodynamic properties recited in claim 20. The district court further explained that Scicinski did not supply any such motivation itself. *Id.* at 201–02. Experts described Scicinski as "aspirational" and "hypothetical" and noted that the reference "would be dismissed" by a skilled artisan. *Id.* We see no error in the district court's finding that while Scicinski disclosed a formulation in the abstract, it did not set forth any pharmacokinetic or pharmacodynamic data or "offer any explanation" as to why the hypothetical formulation would achieve the disclosed properties. *Id.* It was therefore unclear whether Scicinski could even achieve the intended clinical effects for the disclosed formulation, much less provide a motivation to further adapt that hypothetical formulation to pursue the combination of elements recited in the claimed invention with a reasonable expectation of success. *Id.*

The district court also considered and rejected Actavis's argument that U.S. Patent Pub. No. 2007/215,511 (Mehta) "taught an artisan of ordinary skill how to develop a liquid formulation of MPH with a single mean peak [pharmacokinetic] profile, 12-hour duration, and 45-minute onset." *Id.* at 199. The district court found that while Mehta generally provides that adjusting the ratios of formulation components can affect pharmacokinetic and pharmacodynamic attributes, Mehta's teachings are at too high a level of generality and thus do not "teach or suggest that one can simultaneously achieve the desired early onset and extended duration of effect while maintaining a single peak [pharmacokinetic] profile." *Id.* Mehta therefore does not supply a motivation to combine with a reasonable expectation of success. *Id.* Actavis has not shown that the district court clearly erred.

Further confirming the district court's conclusion is evidence that there was a long-felt, unmet need for a liquid

formulation having the claimed pharmacokinetic and pharmacodynamic properties. *Id.* at 200–01. Since the development of MPH in the 1950s, none of the many iterations accomplished the desired liquid formulation with both an early onset and extended release. *Id.*

Because the district court's fact-findings are not clearly erroneous and we see no legal error in the analysis, we affirm the district court's decision that claim 20 of the '765 patent would not have been obvious over the asserted references based on lack of evidence of a motivation to combine with a reasonable expectation of success.

2. Early T_{max} Claims

The district court found that Actavis's arguments regarding motivation to combine with a reasonable expectation of success were similarly lacking for the group of claims directed to a T_{max} of about 4 to 5.25 hours but not a 45-minute onset. For this group of claims, Actavis again relied on Scicinski disclosing the claimed formulation. *Id.* at 201. However, as described above, Scicinski did not disclose a liquid formulation for which there was a long-felt unmet need, and Scicinski presented only a hypothetical formulation without any data or explanation for why or how a formulation with the claimed limitations could be accomplished. *See id.* at 202 ("Scicinski did not offer any explanation about why he thought his formulation could achieve a combined single mean peak with 12-hour duration and a T_{max} range of about 4 to 5.25 hours."). Accordingly, we also affirm the district court's decision that claim 6 of the '765 patent, claim 4 of the '033 patent, and claims 15, 16, and 20 of the '390 patent would not have been obvious because the district court did not clearly err in finding that Actavis failed to show a motivation to combine with a reasonable expectation of success.

3. 45-Minute Onset and Early T_{max} Claims

Because the parties agree that whether claim 10 of the '033 patent, claiming both a 45-minute onset and the early T_{max} range, would have been obvious rises and falls with the obviousness determinations of the other two claim groups, we affirm the district court's decision that claim 10 would not have been obvious. Appellant's Br. 58–59; Appellee's Br. 59–60; *Remand Decision* at 203.

CONCLUSION

We have considered Appellant's remaining arguments and do not find them persuasive. For the foregoing reasons, we affirm.

AFFIRMED