NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

TRIS PHARMA, INC.,
Plaintiff-Appellant

v.

ACTAVIS LABORATORIES FL, INC.,
Defendant-Appellee

2017-2557, 2017-2559, 2017-2560

Appeals from the United States District Court for the District of Delaware in Nos. 1:14-cv-01309-GMS, 1:15-cv-00393-GMS, 1:15-cv-00969-GMS, Judge Gregory M. Sleet.

OPINION ISSUED: November 20, 2018
OPINION MODIFIED: January 16, 2019*

ERROL TAYLOR, Milbank, Tweed, Hadley & McCloy, LLP, New York, NY, argued for plaintiff-appellant. Also

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* This opinion has been modified and reissued following a petition for panel rehearing filed by Actavis Laboratories FL, Inc.

represented by ANNA BROOK, JORDAN P. MARKHAM, FREDERICK ZULLOW.

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Before NEWMAN, O'MALLEY, and CHEN, *Circuit Judges.*

CHEN, *Circuit Judge.*

Tris Pharma, Inc. (Tris) holds the approved New Drug Application for Quillivant XR®, an extended release methylphenidate (MPH) formulation for the treatment of Attention Deficit Hyperactive Disorder (ADHD). When Actavis Laboratories, Inc. (Actavis) submitted an Abbreviated New Drug Application (ANDA) to the U.S. Food & Drug Administration (FDA) seeking approval to market generic versions of Quillivant XR®, Tris sued Actavis for infringement of U.S. Patent Nos. 8,465,765 ('765 patent), 8,563,033 ('033 patent), 8,778,390 ('390 patent), 8,956,649 ('649 patent), and 9,040,083 ('083 patent). After a five-day bench trial, the district court found all asserted claims of the patents-in-suit invalid under 35 U.S.C. § 103. Tris appealed. Because the district court's conclusions of law are based on inadequate fact-findings, we vacate and remand.

BACKGROUND

MPH is one of the most widely prescribed psychostimulants and has been used to treat ADHD since the mid-1950s. Early formulations of MPH were immediate release (IR) forms of the drug that exhibited clinical benefits within 20 to 60 minutes after dosing and whose

effects lasted 2–4 hours. IR forms of MPH, however, had drawbacks because they had to be administered multiple times a day, making it challenging for patients to adhere to the dosing schedule. Sustained release (SR) formulations of MPH were thus developed and available in the early 1980s for greater dosing convenience and patient compliance. But those first-generation SR formulations had their own shortcoming: a slow onset of action. Tris's Quillivant XR® is an extended release formulation of MPH comprising an IR component and a SR component. It is a formulation that achieves a 45-minute therapeutic onset and 12 hours of therapeutic effect.

Actavis challenged the validity of twenty-one claims from five patents at the district court, which found all these claims invalid under 35 U.S.C. § 103. On appeal, Tris requests that we reverse the district court's judgment for seven claims in three patents: '765, '033, and '390 patents. These seven appealed claims are: claims 4 and 10 of the '033 patent; claims 6 and 20 of the '765 patent; and claims 15, 16, and 20 of the '390 patent. All of the appealed claims are directed to pharmacokinetic (PK) and pharmacodynamic (PD) properties of the Quillivant XR® extended release formulation.[1] These properties include: (1) an extended duration of action of about 12 hours; (2) a single mean peak PK profile; (3) a T_{max} of about 4 to 5.25

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[1] Pharmacokinetics is the study of what a person's body does to a drug after administration. PK values are measurements of a drug's behavior in a patient's blood plasma. One such value relevant for this appeal, T_{max}, represents the time after administration when the maximum concentration of the drug in the blood plasma (C_{max}) occurs. The shape of the PK profile, which reflects the plasma concentration of the drug in the patient's body over time, is also an issue in dispute in this case.

hours (early T_{max}); and (4) a 45-minute onset of action/therapeutic effects. All of the claims on appeal recite, among other properties, a single mean peak PK profile and 12-hour duration of effect limitation. All of the claims except for claim 20 of the '765 patent recite the early T_{max} limitation, and claim 10 of the '033 patent and claim 20 of the '765 patent are the only two claims that require a 45-minute onset of action. Claim 10 of the '033 patent is thus the only asserted claim that recites all four properties.

A. Prior Art

The district court found that the various combinations of the PK characteristics (single mean peak and early T_{max}) and PD characteristics (a 45-minute onset of action and a 12-hour duration of effect) claimed in the patents-in-suit would have been obvious over the prior art. The prior art consists of a number of commercially available, second-generation, extended release formulations of MPH including Concerta®, Daytrana®, Focalin XR®, Metadate CD®, and Ritalin LA®;[2] scientific articles; and U.S. Patent Application Publication No. 2010/0260844 (Scicinski). Below, we briefly describe the prior art relevant to this appeal.

Concerta® is an extended release MPH tablet with a 12-hour duration of effect. J.A. 18, 23. The parties dispute whether or not Concerta® exhibits the single mean peak PK profile limitation because its plasma concentra-

[2] The district court also listed Methylin ER as a commercially available controlled-release formulation. J.A. 16. Confusingly, it later presented PK data for Methylin Oral Solution. J.A. 22. We decline to discuss the Methylin prior art reference because it is unclear on which version the district court is relied.

tion profile exhibits a sharp initial increase followed by a second increase. J.A. 19, 25. The parties also dispute whether Concerta® exhibits a 45-minute onset of action. Tris's expert testified that the clinical efficacy study he performed showed that Concerta® has a 2-hour onset of action, J.A. 2213–14, while Actavis's expert testified that second-generation products like Concerta® generally have an onset of action between 30 minutes to 2 hours. J.A. 2069. Concerta® has a later T_{max} of around 6.8 ± 1.8 hours. J.A. 2098.

Daytrana® is an MPH patch that exhibits a single mean peak PK profile and a 12-hour duration of effect. J.A. 2215, 2069. However, Daytrana® has a 2-hour onset of action, and the record as to its T_{max} is unclear. J.A. 2069.

Focalin XR® is an extended release MPH capsule. While it achieves the claimed 12-hour duration of effect, JA 2069, and 45-minute onset of action, J.A. 3923, its PK profile does not exhibit a single mean peak, and it exhibits a later T_{max} around 6.5 hours. J.A. 2080, 2214–15, 2297. Moreover, Tris notes that Focalin XR® only consists of a single enantiomer *d*-MPH as the active ingredient whereas Quillivant XR® and the appealed claims include both enantiomers.

Metadate CD® is a capsule version of MPH. J.A. 19. While it has an early T_{max} of about 4.5 hours, J.A. 2297, and a 45-minute onset of action, J.A. 2069, the parties disagree as to whether its PK profile exhibits a single mean peak and whether it has a 12-hour duration of effect. J.A. 22–23. Like Concerta®, Metadate CD®'s PK profile exhibits a sharp initial increase followed by a second increase in MPH levels at a later time. J.A. 19. As for its duration of effect, Tris presented testimony that Metadate CD®'s effects only last 6 to 8 hours. J.A. 2069, 2204.

Ritalin LA® is a capsule version of MPH. J.A. 21. Ritalin LA® exhibits an early T_{max} at 5.5 hours and an early onset of action. J.A. 2069, 2099. Its PK profile exhibits two peaks (bimodal), J.A. 2615, and it only has 6–8 hours of effect. J.A. 2069.

Scincinski describes a formulation of MPH that provides a rapid onset of action within 1 to 1.5 hours, a single T_{max} of 5.5 to 7.5 hours, and a therapeutic duration of about 12 to 14 hours. J.A. 3644.

B. District Court Opinion

Actavis characterized Scincinski as well as the Daytrana®, Concerta®, and Metadate CD® formulations as all disclosing a single mean peak PK profile, exhibiting an early onset of action, and exhibiting an extended duration of effect. This, Actavis argued, would have suggested to a skilled artisan that a single mean peak PK profile could provide the claimed early onset of action and extended duration of effect. Tris disagreed for two primary reasons.

First, the prior art formulations were developed using two components: IR and ER formulations of MPH. These two components together in a formulation typically resulted in two peaks, or a bimodal profile, with the first peak resulting from the IR component of the formulation and the second from the ER component. Further, Tris asserted that this bimodal profile was important to counteract "acute tolerance" or "tachyphylaxis." Acute tolerance is the theory that as the day progresses, higher levels of the drug in the blood are required to produce the same therapeutic effects. Thus, in order to achieve sustained effects, the formulations in the prior art, according to Tris, were designed to mimic the peaks and valleys of multiple immediate release dosing regimens—one peak for the IR formulation and a second peak for the ER formulation.

Second, Tris argued that prior art formulations of MPH have a late T_{max} to achieve the sustained duration of action. To support this position, Tris pointed to Metadate CD® and Ritalin LA®, both of which have an early T_{max} but a shorter duration of action of around 6 to 8 hours. Concerta®, on the other hand, achieves the 12-hour duration of effect but has a later T_{max} that is outside the claimed range of about 4 to 5.25.

The district court stated that, "[w]hile [it] believe[d] Tris'[s] evidence regarding the second generation products [wa]s persuasive, it [wa]s not dispositive on the obviousness inquiry." J.A. 39. Rather, the district court found that Daytrana® clearly exhibits a single mean peak PK profile, and thus Actavis had demonstrated that a prior art reference taught this particular claim limitation.

Importantly, the district court found that Scicinski describes an oral form of MPH with a long duration of action, rapid onset, and a single mean peak PK profile. The district court reasoned that a skilled artisan would have undoubtedly looked to Scicinski when formulating an extended release MPH drug because Scicinski's purpose of a fast onset, long-lasting MPH formulation aligned with what the parties agreed a skilled artisan would have been motivated to achieve. The district court acknowledged that Scicinski describes a hypothetical product but declined to discount Scicinski simply because it contains a prophetic example. The district court also credited Actavis's expert's testimony that skilled artisans would have used the known technique of deconvolution to achieve a product that meets the target PK profile like that described in Scicinski:

> Q: Now, once a person of ordinary skill in the art has decided on a target PK profile, at a very general level, what are the next steps towards making a product?

> A: Okay. The next steps would be to take this pharmacokinetic profile, this plasma profile and, utilizing certain mathematical techniques that are known as deconvolution, separate out the profile into its elimination characteristics and its absorption characteristics, and once you define then simply the absorption characteristics of that product, then you can design a product that has dissolution characteristics that could match then the absorption characteristics that you get by doing this deconvolution technique.

J.A. 40 (citing J.A. 2095).

Further, the district court appeared to credit Actavis's expert's testimony regarding the relationship between T_{max} and duration of effect. Actavis's expert testified that a skilled artisan would not have targeted a specific T_{max} because that parameter does not control the onset or duration of the drug. He noted, moreover, that the claimed T_{max} ranges in the prior art of 4.4 to 7 hours overlapped with the claimed range of 3.6 to 5.78 hours, taking into account the court's construction of "about."

The district court then addressed Tris's expert's testimony that a skilled artisan would not have expected a formulation with a single mean peak PK profile to achieve both early onset and extended duration of action. Because Tris's expert testified that he would defer to a formulator in terms of what sort of PK curve could be achieved, the district court found Actavis's formulator's expert testimony that a skilled artisan would have no trouble achieving early onset of action and extended duration of effect with a single mean peak PK profile persuasive. The district court ultimately found that "Tris'[s] nonobvious[ness] argument hinges primarily on the [single peak] plasma profile and fails to sufficiently weigh the pharmacokinetic details that would have been

known to skilled artisans or the prior art teachings that disclosed how to optimize an MPH product." J.A. 42.

The district court then examined objective indicia of nonobviousness, including unexpected results, long-felt need, commercial success, and copying. As to unexpected results, the district court held that Tris failed to demonstrate that the Quillivant XR® formulation exhibited some superior property or advantage that a skilled artisan would have found surprising or unexpected. J.A. 45 (citing *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 997 (Fed. Cir. 2009)). Tris argued that its formulation unexpectedly provided (1) a 45-minute onset of action and a 12-hour duration of effect with a single mean peak PK profile and (2) a 12-hour duration of effect with an early T_{max} of about 4 to 5.25 hours. The district court found these arguments irrelevant because Tris had not performed the proper comparison to the closest prior art. *Id.* (citing *Kao Corp. v. Unilever U.S. Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006)). And even considering Tris's unexpected results argument, the district court observed that the prior art would have led a skilled artisan to expect that a single peak PK profile could provide for rapid onset and extended duration of action. Thus, the district court concluded that Quillivant XR®'s 12-hour duration of effect and single mean peak PK profile was not unexpected.

Regarding long-felt need, the district court found that the claimed Quillivant XR® formulation did not serve a long-felt but unmet need. The district court pointed to Tris's own expert testimony that Metadate CD®, Ritalin LA®, and Concerta® had already achieved the goal of once daily dosing. Additionally, Tris's expert also testified that some second-generation MPH formulations could have an onset of action in as early as 30 minutes. J.A. 2069. And while Tris's expert testified that there was a long-felt need for a drug for children who had trouble swallowing pills that the Daytrana® patch did not meet due to skin

irritation issues, J.A. 2272, the district court found that his own writings undermined this contention. J.A. 47 ("This contention is undermined by Dr. McGough's own writings where in the book he authored entitled 'ADHD,' the doctor writes that Daytrana is a product that is 'particularly useful when swallowing is difficult.'").

As to commercial success, the district court found that Tris's evidence only showed a modest level of commercial success. Finally, the district court found that evidence of copying was not compelling.

Accordingly, the district court found all of Tris's asserted claims invalid for being obvious over the prior art. Tris appealed. We have jurisdiction pursuant to pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

"Obviousness is a question of law based on underlying findings of fact." *Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1327 (Fed. Cir. 2009) (citing *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009)). We review the district court's conclusions of law de novo. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1372 (Fed. Cir. 2017). And we review the district court's factual findings for clear error. *Par Pharm. Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014).

Under Fed. R. Civ. P. 52(a)(1), "[i]n an action tried on the facts without a jury or with an advisory jury, the court must find the facts specially and state its conclusions of law separately." Rule 52(a) lays out the separate and distinct roles of the trial and the appellate court. "[F]actfinding is the basic responsibility of district courts, rather than appellate courts. *Pullman-Standard v. Swint*, 456 U.S. 273, 291–92 (1982) (citing *DeMarco v. United States*, 415 U.S. 449, 450 n.* (1974)). A court of appeals should not resolve in the first instance a factual dispute which has not been considered by the district

court. *See id*. "When the opinion explaining the decision lacks adequate fact-findings, meaningful review is not possible, frustrating the very purpose of appellate review as well as this court's compliance with its statutory mandate." *Gechter v. Davidson*, 116 F.3d 1454, 1457 (Fed. Cir. 1997) (citation omitted). Findings of fact are adequate when "they are sufficiently comprehensive and pertinent to the issue to form a basis for the decision." *Medtronic, Inc. v. Daig Corp.*, 789 F.2d 903, 906 (Fed. Cir. 1986) (quoting *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 873 (Fed. Cir. 1985)). Although Rule 52(a)(1) does not require detailed factual findings on every issue raised, it does require findings on "as many of the subsidiary facts as are necessary to disclose to the appellate court the steps by which the trial court determined factual issues and reached its ultimate conclusions." *Atlantic Thermoplastics Co., Inc. v. Faytex Corp.*, 5 F.3d 1477, 1479 (Fed. Cir. 1993).

Tris raises three primary issues on appeal. First, Tris argues that a skilled artisan would not have reasonably expected to successfully combine the claimed single mean peak PK profile with the claimed 45-minute onset of action and 12-hour duration of effect (PD characteristics) because the PK-PD relationship was unknown.[3] Second,

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[3] On appeal, Tris cites *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, as being on all fours with this case. 676 F.3d 1063 (Fed. Cir. 2012). In *Cyclobenzaprine*, we reversed the district court's judgment of obviousness, holding that its "failure to appreciate the lack of a known PK/PD relationship for *any* formulation of cyclobenzaprine rendered deficient its analysis of the evidence . . . and its analysis of the implications of that evidence on its legal conclusions of obviousness." *Id*. at 1071. However, in *Cyclobenzaprine*, no

Tris contends that the district court failed to address why the combination of an early T_{max} and a 12-hour duration of effect would have been obvious. Third, Tris claims the district court mistakenly disregarded Tris's evidence of unexpected results based on a belief that Tris's experts did not compare the claimed invention to the closest prior art. Rather, Tris compared the Quillivant XR® formulation with the commercially available prior art formulations identified by the parties.

As we explain below, the district court failed to make the necessary factual findings and provide sufficient analysis of the parties' arguments to permit effective appellate review. Specifically, the district court's opinion merely recites the parties' arguments but fails to explain or identify which arguments it credits or rejects. We thus cannot reach the merits of whether the Quillivant XR® formulation would have been obvious over the prior art. Rather, we identify gaps in the district court's opinion and remand for the district court to conduct further fact-findings and detailed analysis consistent with this opinion.

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extended release formulation of the drug was present in the prior art, and we found that without a known PK/PD relationship, "immediate-release PK values are of little use in calculating extended-release values, because there is no proof that a skilled artisan would expect the extended release values to produce a therapeutic effect solely because they are drawn from immediate-release values." *Id.* The present case is different because the prior art disclosed numerous existing extended-release formulations, some with one or a combination of single mean peak PK profile, extended duration, early onset, and early T_{max}. *Cyclobenzaprine* is thus, factually distinguishable from this case.

A. Single Mean Peak PK Profile, 45-Minute Onset, and 12-Hour Duration of Effect

Claim 10 of the '033 patent and claim 20 of the '765 patent require a liquid MPH formulation with (1) a single mean peak PK profile, (2) a 45-minute onset of action, and (3) a 12-hour duration of effect. '033 patent col. 38 ll. 34–35; '765 patent col. 39 ll. 16–17. The district court held that a skilled artisan would have found it obvious to use a formulation with a single mean peak PK profile to achieve a 45-minute onset of action and a 12-hour duration of effect. But the district court failed to make adequate findings of fact to support this holding.

First, while the district court found that one would have expected from the prior art that a single mean peak PK profile could provide for rapid onset of action and extended duration of effect, J.A. 46, it never articulated which prior art references do so and how. The district court's only clear finding on this point was its statement that formulations in the prior art such as Daytrana® exhibit a single mean peak PK profile. J.A. 37. The district court also recited Actavis's expert's testimony that Concerta® and Metadate CD® also have a single mean peak PK profile, despite having a slight initial peak or shoulder in their plasma concentration profiles followed by a larger single peak, and that Scicinski also teaches a single mean peak PK profile. J.A. 37, 41.

But it is unclear if these statements amount to actual fact-findings as opposed to a mere recounting of Actavis's arguments. Even if we were to interpret these statements as findings of fact, there are still holes in the district court's analysis. For instance, the district court never made explicit findings that Daytrana®, Concerta®, Metadate CD®, and/or Scicinski also teach a 45-minute onset of action and 12-hour duration of effect. And with respect to the 45-minute onset of action limitation, the district court cited a concession by Tris's expert that second-generation

MPH formulations could have an onset of action in as early as 30 minutes, but it did not explain the significance of this concession.[4] J.A. 47. And the district court did not specifically identify which second-generation products have an onset of action around 30 minutes or state whether it believed that all second-generation MPH products, except Daytrana®, had this onset of action time. As for the 12-hour duration of effect limitation, the district court's opinion is vague as to whether any of the prior art formulations actually teach the 12-hour duration of effect limitation. Throughout its analysis, the district court imprecisely states that certain prior art discloses "efficacy that last[s] throughout the day," a "long duration of effect," or an "extended duration of action." *See e.g.*, J.A. 16, 36, 46. It is unclear, however, whether the district court intended this language to equate to the claimed 12-hour duration of effect. We identify these issues

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[4] Actavis argues that the Biederman article, a prior art reference relied upon by Tris's expert, describes Concerta® as having an onset of action in as early as 30 minutes and a 12-hour duration of effect. J.A. 3446 (Biederman, J. "New-Generation Long-Acting Stimulants for the Treatment of Attention-Deficit/Hyperactivity Disorder," Medscape Psychiatry 8(2) (Nov. 2003)). However, the district court never cited this passage in its opinion as teaching both a 30-minute onset of action and a 12-hour duration of effect. Also, the record is unclear as to whether Scicinski actually teaches the 45-minute onset of action limitation. Scicinski reports that its formulation would be effective "within about 1 to 1.5 hours post administration." '844 application ¶ 0016. While Actavis's expert testified that a skilled artisan would have viewed this disclosure as consistent with a 45-minute onset, the district court never directly made this fact-finding. J.A. 2102.

because whether a particular prior art formulation achieves a 45-minute onset of action and/or a 12-hour duration of effect are central, disputed issues on appeal. And it is the role of the district court to resolve these specific fact issues with an explanation to support those findings.

Second, and importantly, the district court does not address a fundamental aspect of the obviousness inquiry—i.e. why a skilled artisan would have been motivated to use a single mean peak PK 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.[5] Tris argued below and to us on appeal that the acute tolerance theory as well as the prior art taught away from using a single mean peak PK profile to achieve a 45-minute onset and a 12-hour duration of effect. According to Tris, the prior art extended release products with a single mean peak PK profile do not achieve either a 45-minute onset of action, a 12-hour duration of effect, or both. Tris argues that this is due to the acute tolerance theory, which postulates that the plasma concentration of a drug must be higher in a patient as the day progresses

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[5] We understand that one of Actavis's arguments on appeal is that Quillivant XR®'s single mean peak PK profile and early T_{max} range are incidental properties of the formulation. That is, these PK limitations played no role in Quillivant XR®'s development. The PK characteristics are specifically claimed in the patents-in-suit, however, and Actavis has not suggested that these limitations are not entitled to patentable weight. Thus, Actavis needs to demonstrate that a skilled artisan would have been motivated to create a liquid formulation of MPH with these claimed PK characteristics and specific PD properties.

to achieve therapeutic efficacy, and therefore a bimodal (two-peak) plasma concentration curve is required. On appeal, Actavis argues that the acute tolerance theory is irrelevant to whether a drug has a single or bimodal peak PK profile, attempts to discredit the theory, and asserts that skilled artisans did not regard the number of peaks as important when formulating a drug. But the district court made none of these findings below. Other than explaining what the acute tolerance theory is, J.A. 38 n.8, and reciting Tris's expert testimony explaining why acute tolerance was one of the reasons a first-generation MPH formulation like Ritalin-SR® could not achieve the desired clinical effects of a fast onset and extended duration, J.A. 38, the district court did not address the acute tolerance theory. It is thus unclear whether the district court found that (1) the theory is not applicable because it does not affect the shape of the plasma concentration curve; (2) the theory is unreliable; or (3) the theory is applicable, but even acknowledging it, a skilled artisan would have a reasonable expectation of success to combine a single mean peak curve with a 45-minute onset of action and a 12-hour duration of effect. And we decline to guess at what the district court meant.

Without the requisite factual findings and adequate explanation for such findings, we cannot affirm the district court's conclusion that a formulation with (1) a single mean peak PK profile, (2) 45-minute onset of action, and (3) 12-hour duration of effect would have been obvious over the prior art. *See Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1061 (Fed. Cir. 2004) ("Because the district court's sparse opinion provides this court with only bald conclusions for review, we conclude that the district court's judgment . . . is insufficient under Rule 52(a). We thus vacate those portions of the district court's opinion and remand those issues to the district court for specific factual findings."); *see also Atlantic Thermoplastics Co.,* 5 F.3d at 1479 (finding the court's

opinion too conclusory and sparse to provide a factual basis for determining whether the invention was on sale within the meaning of 35 U.S.C. § 102(b)). Accordingly, we remand this issue to the district court for further fact-finding.

B. Early T_{max} and 12-Hour Duration of Effect

Claims 4 and 10 of the '033 patent; claim 6 of the '765 patent; and claims 15, 16, and 20 of the '390 patent recite a liquid formulation of MPH with a single T_{max} of about 4 to 5.25 hours and a 12-hour duration of effect. '033 patent col. 38 ll. 3–5, 34–35; '765 patent col. 38 ll. 4–13; '390 at col. 39 ll. 3–11, 27–29. On appeal, Tris argues that the district court never provided its assessment of the obviousness of a MPH formulation with both an early T_{max} and 12-hour duration of effect. We agree.

The district court's analysis with respect to T_{max} is very cursory. The entirety of the district court's discussion of T_{max} appears amounts to a mere recitation of Actavis's experts' testimony regarding how (1) T_{max} does not control the onset or duration of effect and (2) T_{max} ranges in the prior art formulations overlap with the claimed T_{max} range of 3.6 to 5.78 hours (factoring in the district court's construction of "about"). J.A. 41. And, yet again, the district court fails to articulate whether it credited this testimony or explain why and how the testimony supports its conclusion. Even if we were to assume that these statements were actual findings of fact, the district court's analysis still fails to explain why a skilled artisan would have reasonably expected to achieve a formulation with the claimed 12-hour duration of effect and an early T_{max}.

The district court's opinion lacks any response to Tris's argument that formulations with an early T_{max} (such as Metadate CD® and Ritalin LA®) did not achieve 12 hours of effect while those with 12 hours of effect (Concerta® and Focalin XR®) had later T_{max} values. Tris's

expert explained that this was because oral formulations only contain a certain amount of any drug; if the formulation releases a substantial amount of the drug to obtain an early T_{max}, then the formulation would not be expected to achieve extended effects for the whole day. J.A. 2204. While Actavis's expert responded to this in his testimony, J.A. 2101, the district court opinion does not discuss or cite Tris's testimony.

As with the single mean peak PK profile, 45-minute onset of action, and 12-hour duration of effect combination of limitations, we also remand the obviousness of the combination of an early T_{max} with a 12-hour duration of effect to the district court for further consideration.

C. Objective Indicia of Nonobviousness

Tris argues on appeal that the district court incorrectly rejected Tris's experts' testimony on unexpected results because they purportedly failed to compare the Quillivant XR® formulation with the closest prior art. We agree. Tris's experts compared the Quillivant XR® formulation to all prior art products whose PK and PD values were cited by Actavis or known to Tris. J.A. 2708–13. While *Kao* stands for the proposition that "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art," we do not read *Kao* so rigidly as to require Tris to identify and focus on just one prior art product when multiple, similar extended release formulations of MPH existed or were described in the prior art. 441 F.3d at 970. Because the patents-in-suit claim multiple PK and PD characteristics, different prior art references are closer on different PK and PD characteristics, and none of the parties asserted that one of the references or products represented the closest art. Under the circumstances here, the district court should have considered Tris's evidence that its claimed invention enjoyed unexpected

properties compared to the known, extended release formulations.

Moreover, even though the district court went on to consider the merits of Tris's unexpected results argument, the district court's analysis is deficient because it, at best, only addresses the single mean peak PK limitation. J.A. 46. The district court does not explain why—separately, and more importantly together with the single mean peak PK profile limitation—the T_{max}, 45-minute onset, and 12-hour duration of effect limitations were not unexpected. Thus, we remand the issue of unexpected results to the district court for further analysis.

Additionally, Tris also argues that the district court incorrectly rejected its evidence of long-felt need based on second-generation products that lack one or more of the long-felt needs Tris identified. Below, Tris argued that there was a long-felt need for a product having several desired properties: (1) a liquid MPH product that does not require swallowing a tablet; (2) a 45-minute onset of action; and (3) 12-hour duration of effect. None of the prior art products, Tris contends, satisfied this alleged long-felt need because none of them possess all three of these properties.

In rejecting Tris's long-felt need argument, the district court opinion identified various prior art products that meet each of the three individual needs above, but never identified a prior art product that contains all three properties. For instance, Daytrana® can be administered to individuals without requiring them to swallow a pill; Metadate CD®, Ritalin LA®, and Concerta® are administered once daily. J.A. 44. The district court also found that second generation prior art products generally have an onset of action of as early as 30 minutes. *Id.* But finding each of the properties in separate prior art products does not adequately address Tris's specific theory as to a long-felt need for all three desired properties to be

contained a single product. Actavis contends that any differences in onset, duration, and formulation between Quillivant XR® and particular prior art products were too insignificant to establish any unsolved long-felt need, but the district court did not make such a finding for us to review. Accordingly, we remand the long-felt need issue to the district court for further consideration.

In view of the errors we identified above, we invite the district court to reconsider all the evidence of objective indicia in its overall determination of obviousness.

CONCLUSION

Because district court's obviousness decision lacks the requisite fact-finding, and because the district court erred in rejecting Tris's evidence of objective indicia of nonobviousness, we remand the obviousness analysis to the district court for further fact-finding. We have considered the parties' other arguments and find them unpersuasive.

VACATED AND REMANDED

COSTS

No Costs.