United States Court of Appeals for the Federal Circuit

UCB, INC., UCB PHARMA GMBH, LTS LOHMANN THERAPIE-SYSTEME AG,
Plaintiffs-Appellants

v.

ACTAVIS LABORATORIES UT, INC.,
Defendant-Appellee

2021-1924

Appeal from the United States District Court for the District of Delaware in No. 1:19-cv-00474-KAJ, Circuit Judge Kent A. Jordan.

UCB, INC., UCB PHARMA GMBH, LTS LOHMANN THERAPIE-SYSTEME AG,
Plaintiffs-Appellants

v.

MYLAN TECHNOLOGIES INC.,
Defendant-Appellee

2021-2336

Appeal from the United States District Court for the District of Delaware in No. 2:19-cv-00128-cr, Circuit Judge Kent A. Jordan.

Decided: April 12, 2023

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

STOLL, *Circuit Judge*.

This appeal concerns the validity of U.S. Patent No. 10,130,589, directed to transdermal rotigotine patches and asserted by UCB, Inc., UCB Pharma GmbH, and LTH

Lohman Therapie-Systeme AG (collectively, "UCB") in Hatch-Waxman proceedings. UCB sued Actavis Laboratories UT, Inc. ("Actavis") for infringement based on Actavis's filing of an Abbreviated New Drug Application. The United States District Court for the District of Delaware found the asserted claims of the '589 patent invalid for anticipation and obviousness. Because the district court's fact findings on overlapping ranges, teaching away, unexpected results, and commercial success are not clearly erroneous, we affirm the judgment of invalidity.

BACKGROUND

I

The drug at issue in this pharmaceutical case is rotigotine, which is used to treat Parkinson's disease. Parkinson's disease is a neurodegenerative disorder that is presently estimated to affect more than a million Americans. Parkinson's disease impacts motor control and causes significant gastrointestinal dysfunction, such as "difficulty swallowing, delayed gastric emptying, and slow transit times through intestines," symptoms that can frustrate oral treatments. J.A. 6488–89, ¶ 81.

The technology at issue relates to transdermal therapeutic systems (TTSs), which deliver drugs through the patient's skin and thus avoid complications with oral treatments. TTSs are usually implemented as skin patches that deliver drugs across the patient's skin barrier to enter the patient's bloodstream. These patches contain drugs in an "amorphous," i.e., non-crystalline, form because drugs in crystalline form cannot cross the skin barrier. Consequently, crystallization in patches can reduce the amount of drug leaving the patch and hence reduce a patient's dose.

Amorphous materials can transition from a non-crystallized (high energy) state to a crystallized (lower energy) state. "[T]he temperature at which an amorphous solid

changes from a rigid state to a flexible, rubbery state" is the glass transition temperature (Tg). *UCB, Inc. v. Actavis Lab'ys UT, Inc.*, No. CV 19-474, 2021 WL 1880993, at *7, ¶ 44 (D. Del. Mar. 26, 2021) (*UCB II*). Above Tg, molecules are more mobile and more likely to crystalize.

In 2007, UCB invented and marketed Neupro® (which we refer to as original Neupro®), the first U.S. Food and Drug Administration approved patch for treatment of Parkinson's disease. Original Neupro® contains a dispersion of amorphous rotigotine and polyvinylpyrrolidone (PVP). PVP stabilizes amorphous rotigotine by increasing the Tg and preventing hydrogen bonding between rotigotine molecules, which prevents a clumping of sorts that creates crystallization. *See id.* at *7, ¶¶ 44, 46. Significant to this appeal, original Neupro® contains a weight ratio of rotigotine to PVP of 9:2. *Id.* at *8, ¶ 57.

Original Neupro® is covered by several UCB patents, including U.S. Patent Nos. 6,884,434 and 7,413,747 (the Muller patents). The Muller patents have materially similar specifications and claim priority to an application filed in 1999. The '434 Muller patent teaches a TTS having rotigotine in an amount effective for treating Parkinson's disease, with PVP in the range of 1.5% to 5% (w/w). *See* '434 Muller patent, col. 7 ll. 55–67, col. 8 ll. 17–22, col. 8 ll. 54–63 (claims 1, 5, 14–15). The '747 Muller patent teaches a TTS with a ratio of 9% rotigotine to 1.5% to 5% PVP by weight. '747 Muller patent, col. 8 l. 66–col. 10 l. 4 (claim 14). The Muller patents also describe an exemplary process for making a TTS with a rotigotine to PVP weight ratio of 9:3 rotigotine to PVP. '434 Muller patent, col. 5 l. 54–col. 6 l. 14 (Example 2); '747 Muller patent, col. 6 ll. 16–44 (Example 2).

II

In August 2007, some three months after the original Neupro® U.S. launch, it was discovered that a new crystalline form of rotigotine—"Form II"—occurred when

rotigotine was stored at room temperature. After discussions with the FDA, UCB recalled original Neupro® from U.S. markets in April 2008. Original Neupro® remained in limited use in the U.S. under a compassionate-use program, while European regulators agreed to continue marketing original Neupro® under cold-chain conditions (i.e., refrigerating original Neupro®), which prevents Form II crystallization.

In 2012, the FDA approved a new version of Neupro® (reformulated Neupro®), which employs a weight ratio of 9:4 rotigotine to PVP. The reformulated Neupro® exhibits long-term stability at room temperature with a two-year shelf-life. Reformulated Neupro® is bioequivalent to the original Neupro®, and the FDA approved it without new efficacy studies. The Muller patents are listed in the FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the Orange Book, as covering reformulated Neupro®.

In 2013, Actavis submitted an Abbreviated New Drug Application (ANDA) to the FDA for approval of a generic version of a transdermal rotigotine patch. In 2014, UCB filed suit for infringement of the '434 Muller patent and U.S. Patent No. 8,232,414. *See UCB, Inc. v. Watson Lab'ys, Inc.*, No. CV 14-1083, 2017 WL 11646645, at *1 (D. Del. Nov. 14, 2017), *aff'd*, 927 F.3d 1272 (Fed. Cir. 2019) (*UCB I*).[1] The district court upheld the validity of the challenged claims of the '434 Muller patent, held some of the challenged claims of the '414 patent invalid under 35 U.S.C. § 102(a), and granted UCB an injunction preventing

[1] Watson Laboratories, Inc. was the named defendant in the original suit, but Actavis (formally known as Watson) became the defendant. *See UCB II*, 2021 WL 1880993, at *1 n.1.

approval of Actavis's ANDA. The injunction expired in March 2021, when the '434 Muller patent expired.

In 2018—while *UCB I* was on appeal—UCB filed the patent application that matured into the patent-in-suit, the '589 patent. The '589 patent claims priority from a provisional application filed in December 2009. The patent is entitled "Polyvinylpyrrolidone for the Stabilization of a Solid Dispersion of the Non-Crystalline Form of Rotigotine" and discusses both rotigotine Form I and Form II. *See* '589 patent, col. 1 ll. 47–54, col. 11 l. 66–col. 12 l. 2. The written description explains that "PVP is unexpectedly able to stabilize the non-crystalline form of rotigotine and prevent rotigotine from re-crystallization in a solid dispersion . . . thereby imparting sufficient long term storage stability properties to the [TTS], preferably at room temperature." *Id.* at col. 3 ll. 28–35. The '589 patent discloses and claims a TTS having a range of rotigotine to PVP ratios by weight of about 9:4 to about 9:6. Claim 1 is representative:

> 1. A method for stabilizing rotigotine, the method comprising providing a solid dispersion comprising polyvinylpyrrolidone and a non-crystalline form of rotigotine free base, wherein the weight ratio of rotigotine free base to polyvinylpyrrolidone is in a range from about 9:4 to about 9:6.

Id. at col. 15 ll. 54–59. The '589 patent's Table 3, shown below, displays results of storage stability testing of samples of rotigotine to PVP ratios ranging from 9:1 to 9:11.

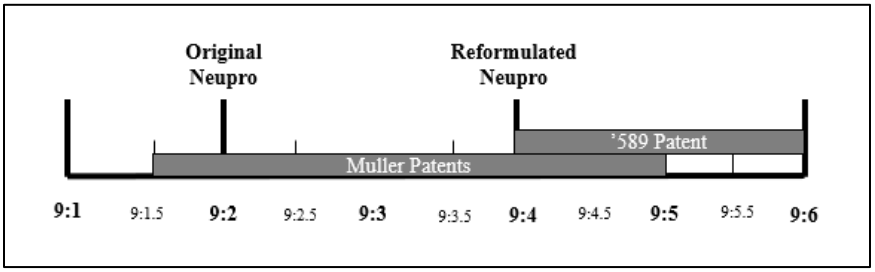
TABLE 3

Results from storage stability testing of sample Nos. 1-9 at 25° C./60% RH (+ = crystals, – = no crystals)

	Sample No.								
	1	2	3	4	5	6	7	8	9
Rotigotine:PVP [weight ratio]	9:1	9:1.6	9:2	9:3	9:4	9:6	9:8	9:11	9:4
0 weeks	+	+	–	–	–	–	–	–	–
1 week	+	+	+	+	–	–	–	–	–
4 weeks	+	+	+	+	–	–	–	–	–
8 weeks	+	+	+	+	–	–	–	–	–

Id. at Tbl. 3. The patent explains that no crystals were observed at room temperature for up to 24 months for sample 5 with the PVP to rotigotine weight ratio of 9:4. *Id.* at col. 15 ll. 17–19.

A comparison of the Muller patents, the '589 patent, and original and reformulated Neupro® is depicted below. As shown, the ranges of rotigotine to PVP ratios disclosed in the Muller patents and the '589 patent overlap from about 9:4 to 9:5 and include the ratio in reformulated Neupro®.



III

In March 2019, about a year before UCB's injunction expired, UCB again filed a lawsuit against Actavis, accusing Actavis's same ANDA of infringement. This time, UCB asserted the '589 patent, which would delay FDA approval of a generic for nine additional years, until the '589 patent

expires in December 2030. UCB asserted that Actavis infringed claims 1–3, 7, and 10–12 of the '589 patent. Actavis conceded that, if the '589 patent is valid, then its ANDA would infringe.

In July 2019, in response to Mylan Technologies, Inc. seeking to market its own generic version of Neupro®, UCB also filed a lawsuit against Mylan alleging infringement of the '589 patent and U.S. Patent No. 10,350,174. *UCB, Inc. v. Mylan Techs., Inc.*, No. 2:19-CV-128, 2020 WL 2300359, at *1 (D. Vt. May 8, 2020). The parties stipulated to adopt, and the Vermont district court adopted, the Delaware judgment, opinion, and trial record. J.A. 67–69. This appeal consolidates both cases.

In March 2021, the month UCB's injunction expired, the district court ruled on Actavis's invalidity defenses. Applying the "at once envisage" framework for anticipation articulated in *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015), the district court found that the Muller patents anticipate all asserted claims. *UCB II*, 2021 WL 1880993, at *20–22. Separately, the district court held that the asserted claims would have been obvious in view of multiple prior art references, including the Muller patents. *Id.* at *23–27.

UCB appeals the district court's anticipation and obviousness determinations. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

On appeal, UCB argues that the district court erred in its anticipation analysis because, contrary to our precedent, it applied *Kennametal* to an overlapping ranges case. Appellant's Br. 36–39. UCB also argues that the district court's obviousness analysis is incorrect because, broadly, the district court (1) impermissibly relied on hindsight in its analysis; and (2) improperly disregarded evidence of

objective indicia of nonobviousness. *See* Appellant's Br. 49–73. We address anticipation first, followed by obviousness.

I

We start with anticipation. UCB argues that the district court committed legal error by applying the wrong law—*Kennametal* and the "immediately envisage" line of cases—in its anticipation analysis. We agree.

To anticipate a claim, a single "prior art reference must disclose each and every element" recited in the claim. *Adasa Inc. v. Avery Dennison Corp.*, 55 F.4th 900, 910 (Fed. Cir. 2022). Whether a prior art reference anticipates a claim is a question of fact. *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 995 (Fed. Cir. 2006). Questions of fact decided by the district court are reviewed for clear error. *Id.* "A finding is 'clearly erroneous' when although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948). A court's application of an improper standard to fact "may be corrected as a matter of law." *United States v. Singer Mfg. Co.*, 374 U.S. 174, 194 n.9 (1963); *see also Walther v. Sec'y of Health & Hum. Servs.*, 485 F.3d 1146, 1152 (Fed. Cir. 2007).

Our precedent sets forth an established framework for analyzing whether a prior art reference anticipates a claimed range. The framework varies depending on whether the prior art discloses a point within the claimed range or discloses its own range that overlaps with the claimed range. If the prior art discloses a point within the claimed range, the prior art anticipates the claim. *See Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015) (citing *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985)). On the other hand, if the prior art discloses an overlapping range, the prior art anticipates the claimed range "only [] if it describes the

claimed range with sufficient specificity such that a reasonable fact finder could conclude that there is no reasonable difference in how the invention operates over the ranges." *Id.* (citing *Atofina*, 441 F.3d at 999; *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012)). In other words, "[o]nce the patent challenger has established, through overlapping ranges, its prima facie case of anticipation, 'the court must evaluate whether the patentee has established that the claimed range is critical to the operability of the claimed invention.'" *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1338 (Fed. Cir. 2020) (quoting *Ineos*, 783 F.3d at 871).

Here, it is undisputed that the Muller patents disclose a range that overlaps with the claimed range. In finding that the Muller patents anticipate the asserted claims of the '589 patent, however, the district court did not apply the traditional framework for analyzing overlapping ranges. Instead, the district court relied on the *Kennametal* "immediately envisage" line of cases to identify discrete points in Muller's range and analyzed those discrete points as a point-within-a-range case. Specifically, the district court relied on testimony from an Actavis expert, Dr. Robin Rogers, that a person of ordinary skill in the art would read Muller's range to teach "a few examples" of TTSs with specific weight ratios, including 9:4 and 9:5 weight ratios of rotigotine to PVP. *UCB II*, 2021 WL 1880993, at *21, ¶ 12 (citing FF[2] ¶ 79 (citing J.A. 1370–71 (Trial Tr. 313:01–314:20))). The district court also relied on another Actavis expert, Dr. Mark Prausnitz, who testified that a skilled artisan would see five or so examples, including "1.5, 2, 3, 4, [and] 5 [and] maybe you would even go to half integers, but a POSA would not expect to look in more granular detail than that to calculate th[e] range"

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[2] Citations to "FF" refer to the paragraphs within the district court's findings of fact.

taught by Muller. J.A. 1428 (Trial Tr. 371:03–10). Based on this testimony, the district court found that "[a] POSA would envisage examples at whole and half integer percentages of PVP and would not look in more granular detail." *UCB II*, 2021 WL 1880993, at *11, ¶ 79. As noted above, the envisage language stems from *Kennametal*, where we held that a reference can anticipate a claim "even if it 'does not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." 780 F.3d at 1381 (cleaned up) (citation omitted). Continuing, the court analyzed this case as a point-within-the-range case—not an overlapping range case—and found that because a person of ordinary skill in the art would readily envisage a combination of 9% rotigotine with 4% or 5% PVP by weight from the range disclosed by Muller, Muller anticipates the '589 claims' recitation of a weight range from "about 9:4 to about 9:6." *UCB II*, 2021 WL 1880993, at *21–22.

UCB argues that the district court erred by ignoring our case law regarding overlapping ranges, which requires considering the criticality of the claimed range. We agree.

The district court's use of the "immediately envisage" line of cases to convert this case into a point-within-a-range case constitutes an improper application of our precedent governing overlapping ranges.[3] We rejected similar attempts to convert the disclosure of a range into the disclosure of individual values in *Ineos*, 783 F.3d at 869. There, we explained that the disclosure of a range is not a

[3] In addition, the court's fact finding that a person of ordinary skill in the art would only consider half and whole integers contradicts the specification of the '589 patent. Table 3 of the '589 patent, for example, discloses a ratio of 1.6, neither an integer nor a half integer.

disclosure of the endpoints of the range or other discrete points within the range. *Id.*

The district court's analysis also improperly extends *Kennametal,* 780 F.3d at 1381–83. As we held in *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274 (Fed. Cir. 2017):

> *Kennametal* does not stand for the proposition that a reference missing a limitation can anticipate a claim if a skilled artisan viewing the reference would "at once envisage" the missing limitation. Rather, *Kennametal* addresses whether the disclosure of a limited number of combination possibilities discloses one of the possible combinations.

Here, the district court's use of *Kennametal*—supporting its finding that Muller's range recites a specific example and thus that the specific example anticipates the entire range recited in the '589 patent claims—goes beyond *Kennametal*'s intended application. We determine that it was legal error for the district court to do so.

Actavis urges us to nonetheless affirm the district court's finding of anticipation because the district court, in effect, conducted the criticality analysis required in overlapping range cases. Appellee's Br. 46–49; *see also Genentech*, 946 F.3d at 1338. Actavis attempts to characterize some of the district court's findings—e.g., that "[t]he 9:4 to 9:6 ratios produce results that are similar in kind to the Prior Art TTS Examples (i.e.[,] 9:2 or 9:3), with similar levels of stability (i.e., lack of crystallization)"—as a finding of criticality for the claimed range of about 9:4 to about 9:6. *See UCB II*, 2021 WL 1880993, at *25, ¶ 44. Even if we saw some merit in Actavis's suggestion, we need not resolve this issue because, as discussed below, we affirm the district court's obviousness determination.

II

We next turn to obviousness. The district court held the asserted claims obvious based on two separate grounds, including that: (1) the claimed range of weight ratios of rotigotine to PVP overlap with that disclosed in the Muller patents and UCB failed to rebut this prima facie case of obviousness; and (2) the prior art's 9:2 and 9:3 TTS examples as modified by Muller's teachings of a range of 1.5% to 5% PVP render the claims obvious.[4] *UCB II*, 2021 WL 1880993, at *23–26. UCB challenges the district court's holdings on both grounds. Because we affirm the judgment of invalidity on the first ground of obviousness, we do not reach the second ground.

The ultimate question of obviousness is a question of law based on underlying fact findings. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1369 (Fed. Cir. 2005) (citation omitted). We review the question of law de novo and the underlying fact findings from bench trials for clear error. *Id.* (citation omitted). "A factual finding is only clearly erroneous if . . . we are left with the definite and firm conviction that a mistake has been made." *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 728 (Fed. Cir. 2017) (citation omitted); *see also Anderson v. City of Bessemer City*, 470 U.S. 564, 574 (1985) ("Where there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous." (citation omitted)). Whether prior art teaches away from the claimed invention, whether the claimed invention is new and unexpected, and "the existence of and weight assigned

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[4] The district court also held the asserted claims invalid under obviousness-type double patenting in view of claims in the Muller patents. *UCB II*, 2021 WL 1880993, at *26–27. Because we affirm the court's obviousness determination, we do not reach its obviousness-type double patenting determination.

to any objective indicia of nonobviousness," like commercial success, "are underlying factual questions we review for clear error." *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1364 (Fed. Cir. 2022) (citing *Merck*, 874 F.3d at 728).

A presumption of obviousness applies "[w]here a claimed range overlaps with a range disclosed in the prior art." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006) (citation omitted). This presumption can be overcome if the "prior art teaches away from the claimed range, . . . the claimed range produces new and unexpected results," or other evidence demonstrates non-obviousness of the claimed range. *Id.* (citation omitted). "A presumption of obviousness does not shift the burden of persuasion to the patentee to prove nonobviousness, but a presumption establishes that, 'absent a reason to conclude otherwise, a factfinder is justified in concluding that a disclosed range does just that—discloses the entire range.'" *Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 272 (Fed. Cir. 2022) (quoting *E.I. duPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018)).

Here, it is undisputed that the range claimed in the '589 patent overlaps with the ranges taught by the Muller patents. Thus, Actavis established a prima facie case of obviousness. On appeal, UCB contends that the Muller patents do not reflect the state of the art at the time of the invention because they precede Form II of rotigotine and, as such, their disclosed range cannot render the claimed range obvious. In addition, UCB contends that one of the district court's fact findings—finding number 80—is inconsistent with its finding of obviousness based on the Muller patents.

Continuing, UCB contends that a different prior art reference—U.S. Patent App. Pub. No. 2009/0299304 (Tang)—is actually the closest prior art because, unlike the Muller patents, Tang addresses the stability problem.

UCB further contends that Tang teaches away from the claimed range, thus establishing nonobviousness of the claimed range. Tang is directed to TTSs with "a therapeutic agent in a stable amorphous form." J.A. 4861, [0002]. It teaches "the importance of the weight ratio of the polymeric stabilizer to the therapeutic agent in stabilizing the therapeutic agent." *Id.* Specifically, Tang taught that if a therapeutic agent has a low Tg, the weight ratio of the polymeric material to the amorphous form of a therapeutic agent is 2 or greater. J.A. 4862, [0030]. And if the therapeutic agent has a high Tg, the ratio is 0.5 or greater. J.A. 4862, [0031]. Tang focused on working examples of scopolamine, which is used to treat motion sickness. *UCB II*, 2021 WL 1880993, at *14, ¶¶ 117–20; *see also* J.A. 4868, [0100]. None of Tang's working examples include rotigotine as the active ingredient. J.A. 4868–70, [0100]–[0105]. And Tang does not disclose the Tg of rotigotine. *See UCB II*, 2021 WL 1880993, at *7, ¶ 45.

In addition, UCB asserted at trial that the claimed weight ratio range of "from about 9:4 to about 9:6" exhibited unexpected results. According to UCB, given the "failure" of the Original Neupro® at 9:2, it was expected that the only slightly larger claimed range of "about 9:4 to about 9:6" would exhibit the same stability failure as the prior art TTS examples. Appellant's Br. 45.

Finally, UCB introduced evidence to establish commercial success and rebut the prima facie case of obviousness. Mainly, UCB introduced evidence of significant sales of reformulated Neupro®. UCB contended that it was entitled to a presumption of nexus between these sales and the claims because the claims are coextensive with reformulated Neupro®. Alternatively, UCB explained that the sales were tied to the claimed range of rotigotine to PVP ratios because "[t]he FDA would not allow Original Neupro® to remain on the market, even under cold-chain storage, due to the formation of crystals." Appellant's Br. 62. And without the alleged invention, UCB argues,

there is no viable product. *Id.* (citing various expert testimony, such as that of Dr. Rahul Guha, who testified that when original Neupro® was off the market, previous patents existed, and the sales were zero).

The district court found that the Muller patents, and not Tang, are the closest prior art. To support this finding, the court reasoned that (1) Tang does not disclose working examples with rotigotine; (2) Tang does not disclose the Tg of rotigotine; and (3) the Muller patents are the closest prior art because, unlike Tang, they disclose and claim a TTS with a range of R:PVP ratios including about 9:4 to 9:5. *UCB II*, 2021 WL 1880993, at *14, ¶¶ 118–20.

Continuing, the district court found that the presumption of obviousness was not overcome based on either the prior art teaching away from the claimed range or new and unexpected results which are "different in kind and not merely in degree." *Id.* at *25, ¶ 44 (quoting *E.I. DuPont*, 904 F.3d at 1006). The district court also found that no other objective indicia of nonobviousness overcame the prima facie case of obviousness. *Id.* at *25, ¶ 42. UCB challenges each of these findings on appeal, and we address each argument in turn below.

A

First, the district court did not clearly err in rejecting UCB's argument that Form II changed the state of the art, thus rendering all pre-Form II prior art, including the Muller patents, irrelevant. As the district court found based on expert testimony and prior art, crystallization in both Form I and Form II occurs due to hydrogen bonding between two rotigotine molecules. As UCB's expert, Dr. Allan Myerson, explained, PVP stabilizes amorphous rotigotine by creating hydrogen bonds with the individual rotigotine molecules, thereby preventing hydrogen bonding between rotigotine molecules and thus preventing crystallization. And while Form II is considered more stable and less soluble than Form I, other evidence, including expert

testimony, indicated that small, rather than systemic, changes to TTSs were needed to achieve stabilization. For example, original Neupro® was still used in the U.S. under a compassionate use program. *UCB II*, 2021 WL 1880993, at *10, ¶ 67. In addition, a medical doctor specializing in Parkinson's disease published an article showing that there were no crystallization issues with original Neupro® when treating over 100 patients. *Id.* at *9, ¶ 65. Finally, Actavis's expert, Dr. Prausnitz, explained how the success of cold-chain storage for original Neupro® in Europe indicated that a "relatively small adjustment" of the of R:PVP ratios was needed. *Id.* at *18, ¶ 149 (citing J.A. 1449–50 (Trial Tr. 392:17–393:04)). In short, we find no clear error in the district court's determination that, due to the similarities in Form I and Form II, no cataclysmic change rendered pre-Form II prior art unusable.

Nor does Finding 80 dictate that pre-Form II prior art should be disregarded and thus that Tang is the closest prior art. Finding 80 states:

> The range of R:PVP ratios in the Asserted Claims in this case and the like range in the Muller Patents' claims significantly overlap and there is no meaningful difference in how a POSA would view them.

Id. at *11, ¶ 80. UCB interprets Finding 80 to mean that "there is no meaningful difference *across* the entire range in Muller." Appellant's Br. 44 (emphasis added). In UCB's view, because original Neupro® (a 9:2 TTS) crystallized, Finding 80 means that a person of ordinary skill in the art at the time of the invention would consider the entire range of 9:1.5 to about 9:6 in the Muller patents similarly flawed. But we read Finding 80 in the context of all the other findings by the district court to simply mean that the claimed range and that in the Muller patents are not patentably distinct. Any confusion about the meaning of this finding is further removed by referencing the district court's record

citation for Finding 80: Actavis's expert, Dr. Prausnitz, testified about the "substantial overlap in the range of 9 to 4 and 9 to 5 *between* [the] two claim sets." J.A. 1455 (Trial Tr. 398:02–09 (emphasis added)). In short, UCB misreads Finding 80—an error infecting much of its obviousness arguments on appeal. As such, Finding 80 does not support UCB's argument that all pre-Form II art should be disregarded and hence, that the district court should have recognized Tang as the closest prior art. Thus, we find no clear error in the district court's contrary findings.

We also see no clear error in the district court's finding on teaching away. A reference teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken." *Galderma Lab'ys., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)). By contrast, a reference does not teach away if it "merely expresses a general preference for an alternative invention but does not 'criticize, discredit or otherwise discourage' investigation into the invention claimed." *DePuy*, 567 F.3d at 1327 (quoting *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004)).

The district court viewed Tang as simply teaching an alternative invention. Indeed, the court acknowledged that Tang could lead a person of ordinary skill to increase the amount of PVP beyond the range of 9:4 to 9:6 ratios of rotigotine to PVP. *UCB II*, 2021 WL 1880993, at *26, ¶ 50. With knowledge of the Tg for rotigotine free base, UCB's expert, Dr. Myerson, testified that Tang teaches a rotigotine to PVP weight ratio of 9:18 for long-term stability. But the district court found that Tang would not dissuade a person of ordinary skill in the art from first trying a weight ratio within the range of 9:4 to 9:6 rotigotine to PVP. *Id.*

In *Galderma*, we held that the district court erred in finding that three prior art references taught away from the claimed invention because they merely taught an alternative composition that "may be optimal or standard" that was not the claimed invention. 737 F.3d at 739. In particular, two of the prior art references mentioned side effects for adapalene concentrations from 0.03% to 0.1% but did not mention the claimed concentration of 0.3% adapalene. *Id.* at 738–39. Nor did the references "indicate in any way that the side effects would be serious enough to dissuade the development of a 0.3% adapalene product." *Id.* at 739. The three references demonstrated that 0.1% was the "standard or optimal concentration of adapalene." *Id.* We held that "teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions." *Id.* Thus, the prior art references did not teach away.

Here, the district court's finding that Tang does not teach away is not clearly erroneous for the same reasons. Tang does not criticize, discredit, or otherwise dissuade a skilled artisan from investigating the claimed range of ratios. In other words, Tang expresses a preference for a higher PVP percentage (a 9:18 rotigotine to PVP weight ratio), but it does not teach away from the claimed range. Contrary to UCB's suggestion, we do not understand the district court's finding that Tang does not teach away as resting on the fact that (1) Tang lacks any reference to the Tg of rotigotine and (2) no working examples include rotigotine in Tang. Instead, we understand the district court to have reasoned that, like the prior art in *Galderma*, Tang does not expressly teach away from the claim invention. Rather, it merely expresses a preference for an optimal concentration (a 9:18 ratio).

Ultimately, even if we saw some merit in UCB's view of the evidence, we do not reweigh the evidence. *See Teva Pharms. USA, Inc. v Sandoz, Inc.*, 574 U.S. 318, 327 (2015) ("A district court judge who has presided over, and listened

to, the entirety of a proceeding has a comparatively greater opportunity to gain . . . familiarity [with specific scientific problems and principles] than an appeals court judge who must read a written transcript or perhaps just those portions to which the parties have referred."). In view of this record, we cannot say that the district court's finding that the prior art does not teach away from the range of 9:4 to 9:6 weight ratio of rotigotine to PVP is clearly erroneous.

B

We next address whether the court erred in finding that UCB had not established unexpected results. Specifically, UCB argues that the lack of crystallization in patches having a rotigotine to PVP weight ratio within the 9:4 to 9:6 weight range is unexpected. This is because, as UCB points out, original Neupro® (which had a 9:2 rotigotine to PVP weight ratio) was the only existing patch within the range of rotigotine to PVP ratios disclosed in the Muller patents—and original Neupro® crystallized. *See* Appellant's Br. 52–53. We are not persuaded by UCB's arguments and conclude that the district court's finding is not clearly erroneous.

"To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (citation omitted). A difference of degree is not as persuasive as a difference in kind—i.e., if the range produces "a new property dissimilar to the known property," rather than producing a predictable result but to an unexpected extent. *Id.* Furthermore, evidence of superior efficacy does not undercut a reasonable expectation of success. *See Hoffmann–La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331, 1333–34 (Fed. Cir. 2014).

The district court found that the claimed range did not produce new and unexpected results. The court determined that results obtained in the alleged invention and those in prior art, like the '747 Muller patent, are "similar in kind . . . [and] with similar levels of stability (i.e., lack of crystallization)." *UCB II*, 2021 WL 1880993, at *25, ¶ 44. We read the district court's finding of similar levels of stability as a finding that any differences in stability between the claimed range and prior art is one of *degree*. Dr. Prausnitz's expert testimony, cited by the court, *id.*, explains that adding slightly more PVP increased stability, but that such a change is one of degree; "there would be no new properties," J.A. 1469 (Trial Tr. 412:07–22).

The court relied on other evidence to support its finding that a person of ordinary skill would expect the claimed rotigotine to PVP weight ratio range and the range disclosed in the prior art to provide stability in a similar way. *See UCB II*, 2021 WL 1880993, at *25, ¶ 46 (citing FF ¶¶ 41–43, 129, 134). For example, the district court cited to prior art and expert testimony showing that PVP was "the most effective crystallization inhibitor" tested. DTX-118 at 118.001; *see also UCB II*, 2021 WL 1880993, at *25, ¶ 46 (citing FF ¶ 41 (J.A. 1405–06 (Trial Tr. 348:09–349:10) (explaining that the chemistry underlying rotigotine/PVP interactions "was very well understood in 2009"); JTX-6 (Schacht) at [0059] (explaining that a "particularly preferred example of . . . a crystallization inhibitor is soluble [PVP]"))).

Further, the court found that a person of ordinary skill would expect that increasing the concentration of PVP in a TTS would increase the stability of the amorphous drug. *UCB II*, 2021 WL 1880993, at *7, ¶ 43. In support of its finding, the court relied on UCB's expert, Dr. Myerson, who testified that, as a general principle, "increas[ing] . . . PVP should increase the stability," although one would need experiments to verify how much the stability increases. *Id.* (citing J.A. 1681–82 (Trial Tr. 583:24–584:14)).

The district court also found that a person of ordinary skill in the art would know that only minor changes to the amount of PVP were needed to address crystallization of original Neupro® given the success with cold-chain storage. *Id.* at *16, ¶ 134. The court cited Actavis's expert, Dr. Rogers, who testified that cold storage helps reduce crystallization of amorphous materials (which occurs when molecules bond to each other), because the cold reduces the mobility of molecules. *Id.* (citing J.A. 1128 (Trial Tr. 109:09–22)). The court also leaned on Actavis's expert, Dr. Prausnitz, who testified that the lack of crystallization at cold temperatures for the 9:2 patch suggests "that a fundamental change in the patch design isn't needed" and, instead, "increasing PVP is going to be something that can get . . . over this hurdle [of crystallization] and increase the stability." *Id.* (citing J.A. 1449–50 (Trial Tr. 392:17–393:04)).

UCB explains that there is clear evidence of unexpected results because "embodiments of the claimed range do inhibit crystals, whereas those immediately neighboring among the Muller range do not." Appellant's Br. 27–28. According to UCB, the district court erred because (1) per Finding 80, a person of ordinary skill would have expected the entire Muller range to crystallize after Form II, Appellant's Br. 52–53; (2) the district court ignores "the crux" of the '589 patent's results—improved long-term, room temperature stability as opposed to stability in general terms, Appellant's Br. 54; (3) the court dismissed evidence of unexpected results solely based on UCB's own internal-confidential efforts of trying a 9:4 patch within weeks of learning of Form II and the crystallization problem, Appellant's Br. 28, 35, 49; and (4) the district court's statement that the range claim was "similar in kind" to the prior art TTS examples "became categorically untrue after Form II appeared," Appellant's Br. 53.

First, as mentioned above, UCB misreads Finding 80. That original Neupro® (9:2) crystallized does not dictate

that a person of ordinary skill in the art at the time of the invention would think that the entire Muller patent range (of about 9:1.5 to 9:5) would crystallize.

Second, UCB's references to "long-term, room temperature stability" reflect UCB's failed claim construction argument. J.A. 1006 n.4; J.A. 1000–10. During claim construction UCB argued that claim 1's "method for stabilizing rotigotine" required it to be "capable of maintaining the non-crystalline rotigotine in noncrystalline form for at least 2 years at room temperature or temperatures not exceeding [25 degrees Celsius]." J.A. 1006 n.4. The district court disagreed, rejecting the importation of a limitation from the specification. *Id.* UCB does not challenge the district court's claim construction on appeal. Accordingly, UCB's argument that the district court ignored long-term room temperature stability fails.

Third, UCB is correct that, under 35 U.S.C. § 103(a), "[p]atentability shall not be negated by the manner in which the invention was made." But the district court did not solely rely on the inventor's path for its factual determination. As noted above, the court relied on scientific principles like the known effects of PVP and expert testimony regarding a difference in "degree." *See UCB II*, 2021 WL 1880993, at *25, ¶¶ 44, 46. Separately, UCB's own expert, Dr. Richard Guy, testified that "a person of ordinary skill in the art would kind of do what LTS and UCB did," J.A. 1850–53 (Trial Tr. 752:04–755:09), and the court did not clearly err in considering such testimony. Accordingly, any error by the district court in this regard was harmless.

Finally, we are not left with a definite and firm conviction that the district court erred in finding that the claimed range was "similar in kind" to the prior art TTS examples even after Form II. As noted above, the court cited Actavis's expert, Dr. Prausnitz, who testified that the change in stability was one of *degree*. *See UCB II*, 2021 WL 1880993, at *25, ¶ 44 (citing J.A. 1469 (Trial Tr. 412:07–

22)). The court also heard UCB's evidence on Form II, including UCB's expert testimony on how Form II changed the state of the art. As discussed above, the district court was entitled to weigh the conflicting expert testimony on this point and did not clearly err in declining to adopt UCB's view.

In sum, the district court's finding that the claimed range did not produce new and unexpected results is not clearly erroneous.

C

Finally, we address whether the district court erred in its analysis of UCB's evidence of commercial success. Specifically, UCB argues that the district court erred in finding no nexus, which led it to disregard the commercial success of reformulated Neupro®. *See* Appellant's Br. 41. We disagree.

We have repeatedly held that evidence of commercial success must have a nexus to the claims to be given weight in an obviousness analysis. In other words, there must be "a legally and factually sufficient connection" between the evidence and the patent claims. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (citation omitted). Simply speaking, there may be many reasons a product is commercially successful; it is only where the success is due to the claimed invention that commercial success can show nonobviousness.

We have recognized that a patentee is entitled to a rebuttable presumption of nexus where the patentee shows that the commercial success is tied to a specific product and that the product is the invention disclosed or claimed. *Id.* (citation omitted). Even if a presumption of nexus is inappropriate, a patentee can prove nexus "by showing that the evidence of secondary considerations is the 'direct result of the unique characteristics of the claimed invention.'" *Id.*

at 1373–74 (quoting *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996)).

Here, the district court held that UCB was not entitled to a presumption of nexus under *Fox Factory* because numerous patents covered Neupro®. *UCB II*, 2021 WL 1880993, at *26, ¶ 53. In the alternative, the district court held that any inference of obviousness from UCB's commercial success evidence is weak because the Muller patents have operated as blocking patents dissuading competitors from developing a rotigotine TTS. *Id.* at *26, ¶ 54. Because the district court did not clearly err in finding UCB's evidence of commercial success weak, we are not persuaded by UCB's arguments on appeal.

As in *Merck* and *Galderma*, the district court was entitled to consider the existence of blocking patents when weighing UCB's evidence of commercial success. In *Merck* and *Galderma*, we held that where market entry by others was precluded due to blocking patents, the inference of non-obviousness of the asserted claims from evidence of commercial success may be weak. *See Galderma*, 737 F.3d at 740 (citing *Merck*, 395 F.3d at 1377). For example, in *Galderma*, we explained that Galderma's earlier patents blocked the market entry of the claimed improvement directed to a particular concentration of adapalene until long after the time of the invention. *Id.* at 740. As such, "no entity other than Galderma could have successfully brought to 0.3% to market prior to [the time of the invention]," and thus the commercial success evidence was of "minimal probative value." *Id.* at 740–41.

Here, the district court found that UCB's Muller patents weakened its evidence of commercial success. *UCB II*, 2021 WL 1880993, at *26, ¶ 54 (quoting *Galderma*, 737 F.3d at 740–41). The district court explained that "the Muller Patents have operated as blocking patents, dissuading competitors from developing a rotigotine TTS, at least until the expiration of the '434 [Muller] Patent." *Id.* (citing

FF ¶¶ 158–61). We cannot say that the court clearly erred in its analysis given its reliance on our precedent and expert testimony. Indeed, the court's fact findings were fully supported by expert testimony from Mr. Ivan T. Hofmann. *Id.* at *19, ¶ 158. Mr. Hofmann, Actavis' economic expert, testified that he identified the Muller patents as blocking patents because the "parameters that existed in prior patents that would deter anyone other than UCB from conceding the alleged invention of the '589 patent." J.A. 1907 (Trial Tr. 809:14–810:17). He opined that "essentially nobody other than UCB ha[d] an economic incentive to have conceived of the alleged invention that's described in the '589 patent." J.A. 1900 (Trial Tr. 802:17–19).

UCB argues that even when existing patents cover a drug, companies still engage in drug development, and the court's analysis would effectively brand all co-owned patents "blocking" patents. Appellant's Br. 63–64 (citing J.A. 1882–86 (Trial Tr. 784:05–788:06)). As an example, UCB cites to the Tang reference as evidence that Mylan sought patent protection for its own transdermal rotigotine system despite the existence of the Muller patents to show that companies engage in drug development despite existing patents covering that drug. Appellant's Br. 64.

We disagree that the court's analysis brands all co-owned patents as "blocking" patents. The court noted that UCB has held exclusive worldwide rights to rotigotine for all therapeutic indications since 1998, *UCB II*, 2021 WL 1880993, at *19, ¶ 159; that until the '434 Muller patent expired, Actavis was enjoined from marketing a generic version of reformulated Neupro®, *id.* at *26, ¶ 53; and cited expert testimony from Mr. Hofmann who explained that the Muller patents would deter anyone other than UCB from developing the alleged invention in the '589 patent, *id.* at *19, ¶ 158 (citing J.A. 1900–01 (Trial Tr. 802:11–803:08)). By contrast, UCB's expert, Dr. Guha, did not analyze whether UCB's multiple patents were responsible for commercial success. *Id.* at *19, ¶ 160. The district court,

in determining that UCB's extensive patent rights reduced the weight of the evidence of commercial success, did not impermissibly create a bright-line rule; instead, it limited its analysis to the specific facts in the record.

UCB essentially asks us to reweigh the evidence, giving greater weight to Tang and Dr. Guha, one of UCB's experts, to find the evidence of commercial success overcomes the prima facie case of obviousness. For example, Dr. Guha explained that there might be an incentive for both a patentee and third party to come to a licensing agreement for a drug protected by patents when a third party "expands the pie" by, for example, creating a better formulation of a drug that expands the product or, here, getting original Neupro® back into the U.S. market. J.A. 1882–86 (Trial Tr. 784:09–788:06). But the district court already considered this testimony and argument, and it is not our province to reweigh evidence under these circumstances. *See Teva Pharms.*, 574 U.S. at 327.

Contrary to UCB's assertions, the district court did consider that reformulated Neupro® allowed UCB to re-enter the U.S. market. The court's assignment of minimal weight to this evidence was not clearly erroneous given evidence that original Neupro® remained in the U.S. market through the compassionate use program. *See UCB II*, 2021 WL 1880993, at *10, ¶ 67.

We also disagree that the district court's decision lacked extensive analysis. UCB alleges, for example, that the district court's statement that the slight adjustment of PVP content in reformulated Neupro® is not what drives demand is conclusory. *See id.* at *19, ¶ 161; Reply Br. 28. But the preceding sentence explains that efficacy and safety of a rotigotine-containing TTS drive sales in reformulated Neupro®. For support, the court cites to Mr. Hofmann, Actavis's expert, who testified that "what's really driving the [relaunch] sales are the safety and efficacy of a transdermal patch with rotigotine in a known weight ratio

that was already known." *See UCB II*, 2021 WL 1880993, at *19, ¶ 161 (citing J.A. 1900–02 (Trial Tr. 802:14–804:10)). Thus, we are unpersuaded by UCB's argument.

As for the rest of the district court's decision, we do not consider it "devoid of meaningful analysis" as UCB argues, citing *OSRAM Sylvania, Inc. v. American Induction Technologies, Inc.*, 701 F.3d 698, 707 (Fed. Cir. 2012). *See* Reply Br. 30. In *OSRAM*, the district court "did not make any specific findings of fact and gave no basis" to understand its prior statement that disputed issues of fact existed. 701 F.3d at 707. The appellee there countered that the findings were "ascertainable from the parties' own arguments," but we held that it was not our role to "scour the record and search for something to justify a [district] court's conclusion." *Id.* In contrast, here, the district court provided over forty pages of specific findings of fact and citations to such findings in its conclusions of law, as discussed above.

In sum, we find that the district court did not clearly err in finding that the evidence of commercial success is weak.

* * *

We have considered UCB's remaining arguments on appeal and find them unpersuasive. In light of the evidentiary record, we do not see any error with the court's conclusion of obviousness based on the Muller patents.

CONCLUSION

For the reasons above, we affirm the district court's judgment that the asserted claims are invalid as obvious.

AFFIRMED