United States Court of Appeals for the Federal Circuit

SALIX PHARMACEUTICALS, LTD., SALIX PHARMACEUTICALS, INC., BAUSCH HEALTH IRELAND LTD., ALFASIGMA S.P.A.,
Plaintiffs-Appellants

v.

NORWICH PHARMACEUTICALS INC.,
Defendant-Cross-Appellant

2022-2153, 2023-1952

Appeals from the United States District Court for the District of Delaware in No. 1:20-cv-00430-RGA, Judge Richard G. Andrews.

Decided: April 11, 2024

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Before LOURIE, CHEN, and CUNNINGHAM, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* LOURIE.

Opinion dissenting-in-part filed by *Circuit Judge* CUNNINGHAM.

LOURIE, *Circuit Judge*.

Salix Pharmaceuticals, Ltd., Salix Pharmaceuticals, Inc., Bausch Health Ireland Ltd., and Alfasigma S.P.A. (collectively, "Salix") appeal from a final judgment of the United States District Court for the District of Delaware holding claim 2 of U.S. Patent 8,309,569, claim 3 of U.S. Patent 10,765,667, claim 4 of U.S. Patent 7,612,199, and claim 36 of U.S. Patent 7,902,206 invalid as obvious. *See Salix Pharms., Ltd. v. Norwich Pharms., Inc.,* No. 20-cv-430, 2022 WL 3225381 (D. Del. Aug. 10, 2022) ("*Decision*").

Norwich Pharmaceuticals Inc. ("Norwich") cross-appeals from an order that issued after the district court concluded that Norwich infringed claim 8 of U.S. Patent 8,624,573, claim 6 of U.S. Patent 9,421,195, and claims 11 and 12 of U.S. Patent 10,335,397 and had failed to prove

that those claims were invalid. That order, contained within the final judgment, instructed the FDA that the effective approval date of Norwich's Abbreviated New Drug Application ("ANDA") may not precede the expiration dates of those claims. J.A. 51. Norwich also cross-appeals from a denial of its motion to modify the final judgment. *See Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, No. 20-430, 2023 WL 3496373 (D. Del. May 17, 2023) ("*Rule 60(b) Order*").

For the following reasons, we affirm.

BACKGROUND

Rifaximin, the active ingredient in Salix's commercial product Xifaxan®, has been widely used as an antibiotic for decades, having been first synthesized in the early 1980s in Italy and approved there as an antibiotic in 1985. *Decision* at *8; J.A. 2532. The FDA approved Xifaxan nearly 20 years later, in 2004, as 200 mg tablets for the treatment of travelers' diarrhea. *Decision* at *1. The FDA subsequently approved 550 mg tablets for hepatic encephalopathy ("HE") in 2010 and for irritable bowel syndrome with diarrhea ("IBS-D") in 2015. *Id.*

Norwich sought to market a generic version of rifaximin and, in 2019, filed an ANDA for 550 mg tablets with the same indications as Xifaxan, certifying pursuant to 21 U.S.C. § 355(j)(2)(vii)(IV) that Salix's rifaximin patents were invalid. Salix timely sued, asserting that Norwich's ANDA infringed dozens of valid, Orange Book-listed patents. By the time of trial, the case had been streamlined to three groups of patents:

- the '573, '195, and '397 patents, directed to treating HE ("the HE patents");
- the '569 and '667 patents, directed to treating IBS-D with 550 mg rifaximin three times a day (1,650 mg/day) for 14 days ("the IBS-D patents"); and,

- the '199 and '206 patents, directed to rifaximin form ß ("the polymorph patents").

Following a bench trial, the district court held that Norwich infringed the HE patents' claims and had failed to establish their invalidity. *Decision* at *10–11. Norwich did not appeal those holdings. The court also held that Norwich's ANDA infringed the IBS-D and polymorph patents, but that those patents' claims would have been obvious over certain prior art. *Id.* at *2–3, 16–17. Salix appealed those invalidity holdings.

As part of the entered judgment, the district court ordered that the effective date of a final approval of Norwich's ANDA should not precede October 2029, which is the latest expiration date associated with the HE patents. J.A. 51. Norwich then amended its ANDA in an attempt to remove the infringing HE indication and moved to modify the judgment under Federal Rule of Civil Procedure 60(b), asserting that the amendment negated any possible infringement. The court denied Norwich's motion, and Norwich cross-appealed.

We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

Salix first contends that the district court's conclusion that the asserted claims of the IBS-D patents were invalid as obvious was reached in error. Subsumed within that challenge is a question of whether or not a background reference discussed by the court was properly established as prior art. Salix also contends that the court erred in holding that the asserted polymorph patent claims were invalid as obvious. Norwich's cross-appeal asserts that the court erred in the phrasing of its order precluding final approval of its ANDA until expiration of the HE patents. Norwich further asserts that the court erred in denying its motion to modify after the ANDA was amended in an attempt to avoid infringement. We address each argument in turn.

I

We turn first to Salix's contention that the district court erred in concluding that the asserted claims of the IBS-D patents would have been obvious over the asserted prior art.

Whether or not a claim would have been obvious is a question of law, based on underlying factual determinations. *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1328–29 (Fed. Cir. 2020). We review the ultimate legal question of obviousness *de novo* and the underlying factual determinations for clear error. *Id.* at 1328. A finding is clearly erroneous only if we are "left with a definite and firm conviction that the district court was in error." *Id.* (citations omitted).

The IBS-D patents are directed to treating IBS-D with 550 mg rifaximin, thrice-daily (1,650 mg/day), for 14 days. For example, claim 2 of the '569 patent depends from claim 1 as follows:

> 1. A method of providing acute treatment for diarrhea-associated Irritable Bowel Syndrome (dIBS) comprising: *administering 1650 mg/day* of rifaximin for 14 days to a subject in need thereof, wherein removing the subject from treatment after the 14 days results in a durability of response, wherein the durability of response comprises about 12 weeks of adequate relief of symptoms.
>
> 2. The method of claim 1, wherein *the 1650 mg is administered at 550 mg three times per day*.

'569 patent, col. 30 ll. 4–12 (emphases added); *see also* '667 patent, col. 46 ll. 29–33, 39–40 (claims 1 & 3, similar). The key limitation on appeal is the dosage amount that appears in the claims: 550 mg, three times per day ("TID"), for a total of 1,650 mg/day.

Norwich challenged the IBS-D claims' validity by asserting as prior art references a clinical trial protocol that had been published on the ClinicalTrials.gov website in 2005 ("the Protocol")[1] and a 2006 journal article ("Pimentel").[2] The Protocol describes a Phase II study evaluating twice-daily doses of 550 mg (1,100 mg/day) and 1,100 mg (2,200 mg/day) for 14 and 28 days for the treatment of IBS-D. *See* J.A. 7051. Pimentel teaches administering 400 mg, TID (1,200 mg/day), for the treatment of IBS,[3] but further opines that the "optimal dosage of rifaximin may, in fact, be higher than that used in our study." J.A. 4644.

The district court found that those two references disclose each and every limitation of the challenged IBS-D claims, and further found that a skilled artisan would have been motivated to combine those two references to arrive at what is claimed with a reasonable expectation of success. *Decision* at *17, *19–20. The court then concluded that the challenged IBS-D claims were invalid as obvious. *Id.* at

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[1] ClinicalTrials.gov, *History of Changes for Study: NCT00269412, Randomized, Double Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Three Different Doses of Rifaximin Administered BID either Two or Four Weeks in the Treatment of Patients with Diarrhea-Associated Irritable Bowel Syndrome* (December 22, 2005); J.A. 7047–55.

[2] M. Pimentel *et al.*, *The Effect of a Nonabsorbed Oral Antibiotic (Rifaximin) on the Symptoms of the Irritable Bowel Syndrome*, 145 ANN. INTERN. MED., 557 (2006); J.A. 4639–46.

[3] Salix did not argue a difference between a motivation to use rifaximin to treat IBS versus IBS-D. *Decision* at *19 n.3. It concedes on appeal that "[r]oughly one-third of IBS patients suffer from IBS-D," Appellants' Br. at 6, and has not otherwise suggested that treatments for IBS would not inform treatments of IBS-D.

*17–22. Salix appeals, asserting that the court erred in finding that a skilled artisan would have had a reasonable expectation of success in using the claimed 1,650 mg/day dosage to treat IBS-D. Appellants' Br. at 39–48. Whether or not there would have been a reasonable expectation of success is a question of fact, *IXI IP, LLC v. Samsung Elecs. Co.*, 903 F.3d 1257, 1262 (Fed. Cir. 2018), which we review for clear error, *Hospira*, 946 F.3d at 1328.

Salix does not appear to dispute the district court's finding that the Protocol and Pimentel "disclose all limitations of the IBS-D claims." *See Decision* at *17. Rather, it contends that even if the asserted combination of references effectively discloses the claimed 1,650 mg/day dosage, there remains insufficient evidence to support a finding of a reasonable expectation of success in using that particular dosage amount. *See*, *e.g.*, Appellants' Br. at 39–40. According to Salix, the highest prior art dosage amount that could have been supported with a reasonable expectation of success was the 1,200 mg/day dose evaluated by Pimentel. *Id.* at 40. We disagree.

The Protocol provides an outline of a planned Phase II clinical trial in which "three different doses (275, 550 and 1100 mg) of rifaximin" were to be "administered BID [*i.e.*, twice-daily] for either two or four weeks in the treatment of patients with diarrhea-associated irritable bowel syndrome." J.A. 7050 (cleaned up). As an outline of that clinical trial plan, the Protocol provides only that those three specific, twice-daily dosage regimens were to be investigated for either two or four weeks. The Protocol does not include any efficacy or safety data, nor does it mention a 1,650 mg/day dose or TID dosing.

Although we have rejected the idea that "efficacy data [are] always required for a reasonable expectation of success," *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019), we are hesitant to conclude as a general matter that the disclosure of a Phase II clinical trial

plan, standing alone, provides an expectation of success sufficient to render obvious a dosage that was not included within the planned clinical trial. *See* Appellants' Reply Br. at 13–14. But the Protocol was not asserted alone; it was asserted in combination with Pimentel.

Pimentel teaches that administration of 400 mg rifaximin, TID (1,200 mg/day), "resulted in greater improvement in IBS symptoms" and "lower bloating score[s] after treatment." J.A. 4639; *see also id.* at 4642–43 (providing supporting data). Pimentel explains that the 400 mg TID regimen was chosen "on the basis of a previous study that demonstrated the efficacy of rifaximin in bacterial overgrowth." *Id.* at 4640. However, Pimentel does not merely provide that daily rifaximin doses of 1,200 mg were likely to be successful in the treatment of IBS. Pimentel further teaches that "[r]ecent data suggest that the *optimal dosage* of rifaximin *may, in fact, be higher* than that used in our study." J.A. 4644; *Decision* at *20 (emphases added).

The district court did not clearly err in finding that a skilled artisan would have looked to both of those references, considered their limits, and had a reasonable expectation of success as to the efficacy of 550 mg TID dosing. The combined message that the skilled artisan would have discerned from the Protocol and Pimentel is that the optimal dosage for treating patients suffering from IBS disorders may be higher than 400 mg TID, and the next higher dosage unit from the Protocol was 550 mg. We see no clear error in the conclusion that there would have been a reasonable expectation of success in administering the claimed 1,650 mg/day to IBS-D patients. Indeed, certainty and absolute predictability are not required to establish a reasonable expectation of success. *See Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 275 (Fed. Cir. 2022) ("A finding of a reasonable expectation of success does not require absolute predictability of success."); *Acorda Therapeutics, Inc. v. Roxane Lab'ys, Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018) ("This court has long rejected a

requirement of conclusive proof of efficacy for obviousness." (cleaned up)).

Moreover, references establishing the background knowledge of a person of ordinary skill in the art are consistent with the reasonable expectation of success provided by the combination of the Protocol with Pimentel. For example, Cuoco[4] teaches the efficacy of 1,200 mg rifaximin/day for 14 days for the treatment of small intestinal bacterial overgrowth ("SIBO"). J.A. 4533. Salix has acknowledged that those of ordinary skill in the art identified "bacterial alterations" as a potential underlying cause for IBS, Appellants' Br. at 7, and the literature[5] describes SIBO as a condition that is "highly prevalent in patients with irritable bowel syndrome (IBS)," such that "SIBO decontamination is associated [with] a significant improvement of IBS symptoms." J.A. 4664. We therefore agree with the district court that references describing the treatment of SIBO would have been pertinent to the skilled artisan's considerations as to what treatments would have a potential for success in treating individuals suffering from IBS.

In addition to Cuoco, Lauritano[6] teaches an increase in rifaximin efficacy for the treatment of SIBO as doses were increased from 600 mg/day to 1,200 mg/day, providing the

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[4] L. Cuoco & M. Salvagnini, *Small intestine bacterial overgrowth in irritable bowel syndrome: a retrospective study with rifaximin*, 52 MINERVA GASTROENTEROL. DIETOL. (2006) 89; J.A. 4533–39.

[5] E. Scarpellini et al., *High dosage rifaximin for the treatment of small intestinal bacterial overgrowth*, 25 ALIMENT. PHARMACOL. THER. 781 (2007); J.A. 4663–67 ("Scarpellini").

[6] E.C. Lauritano et al., *Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth*, 22 ALIMENT. PHARMACOL. THER., 31 (2005); J.A. 7267–71.

trend that Pimentel described as indicating that doses higher than 1,200 mg/day may be even more optimal for the treatment of IBS. J.A. 7267 ("Higher doses of rifaximin lead to a significant gain in terms of therapeutic efficacy in [SIBO] eradication without increasing the incidence of side-effects."); *see also id.* at 4644. As evidenced by Scarpellini and Lin,[7] those in the art advanced on those findings, and subsequently evaluated higher doses. For example, Scarpellini reported that a 1,600 mg/day dose "showed a significantly higher efficacy" compared with 1,200 mg/day for the treatment of SIBO. J.A. 4663; *see also id.* at 4666 (Table 1, noting study patients included those suffering from IBS-D); *id.* at 4747 (teaching that "[a]bout 400 to about 600 mg of rifaximin may be administered TID for about 10 days" (*i.e.*, 1,200 mg/day to 1,800 mg/day) for the eradication of bacterial overgrowth).

The record further supports the finding that there would have been a reasonable expectation of success in administering higher doses of rifaximin without an intolerable increase in negative side effects. For example, Cuoco teaches that rifaximin was understood as having "a low risk of causing microbial resistance," J.A. 4533, and that rifaximin was well known for its "profile of tolerability and safety widely described in the literature," *id.* at 4538. Scarpellini further reported that the 1,600 mg/day dose provided a "similar compliance and side-effect profile" compared with the 1,200 mg/day dose. *Id.* at 4663. As the district court noted, the "[w]idespread off-label use" of rifaximin also supported the conclusion that rifaximin was safe and effective "for the treatment of IBS-D with a reasonable expectation of success." *Decision* at *19; *see also* Appellants' Br. at 17 ("There is no dispute that skilled

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[7] International Patent Application Publication 2006/102536; J.A. 4721–47.

artisans knew of the general concept of trying off-label use of rifaximin to treat IBS-D.").

In view of the record before us, we see no clear error in the finding that a skilled artisan would have had a reasonable expectation of success in administering the claimed 1,650 mg/day regimen for the treatment of IBS-D. We therefore affirm the district court's holding that the challenged IBS-D claims would have been obvious over the cited references. *See In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (citation omitted)).

Salix further contends that a Press Release[8] issued by Salix in a filing with the Securities and Exchange Commission less than a year before the patents' priority date was not prior art because Norwich failed to establish that it was "by others" as required by pre-AIA 35 U.S.C. § 102(a). Appellants' Br. at 30–39. According to Salix, the district court's inclusion of that allegedly non-prior art reference in its discussion of the skilled artisan's expectation of success was harmful error. *Id.*

Although the district court cited the Press Release in its discussion of the skilled artisan's expectations, it ultimately held that the "Protocol and Pimentel [] disclose all limitations of the IBS-D claims" and that a skilled artisan "would have been motivated to combine the . . . Protocol and Pimentel [] with a reasonable expectation of success." *Decision* at *17. We therefore need not decide whether or not the Press Release was prior art because, even assuming that it was not, the Protocol and Pimentel alone established the obviousness of the claims.

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[8] Salix Pharms., Ltd., Current Report (Form 8-K) (Sept. 5, 2007); J.A. 7477–82.

We accordingly affirm the district court's determination that Norwich established that the IBS-D claims would have been obvious in view of the Protocol and Pimentel.

II

We next turn to Salix's contention that the district court clearly erred in finding that there would have been a reasonable expectation of success in obtaining the rifaximin form ß recited in the polymorph patents' claims.

Whether or not there would have been a reasonable expectation of success is a question of fact, *IXI IP, LLC v. Samsung Elecs. Co.*, 903 F.3d 1257, 1262 (Fed. Cir. 2018), which we review for clear error, *Hospira*, 946 F.3d at 1328. We review the ultimate conclusion of obviousness *de novo*. *Id.*

The polymorph patents are directed to rifaximin form ß. For example, claim 4 of the '199 patent recites:

> 4. Rifaximin in polymorphic form ß, wherein the rifaximin has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9°2θ and wherein the rifaximin has a water content of greater than 5%.

'199 patent, col. 10 ll. 24–27; *see also* '206 patent, col. 11 ll. 33–37, 41–43 (claims 34 & 36, similar).

Norwich challenged the polymorph claims' validity by asserting, *inter alia*, Cannata,[9] which discloses that rifaximin exists in crystalline form with "outstanding antibacterial properties." J.A. 4528; *Decision* at *6. Cannata does not discuss rifaximin's crystal structure in detail, but it does disclose several preparation protocols for rifaximin that include solvents used for crystallization. J.A. 4529–31; *see also id.* at 3408.

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[9] U.S. Patent 4,557,866; J.A. 4526–32.

The district court held that expert testimony supported a conclusion that, in view of the prior art, (1) a skilled artisan would have had good reason to characterize the crystalline rifaximin obtained by following the Cannata protocols, (2) that such characterization was routine and could have been performed "in one day," and (3) that doing so would have led the skilled artisan to have "detected rifaximin ß." *Decision* at *6–7. The district court subsequently concluded that the challenged polymorph claims would have been obvious over the asserted prior art in view of the common knowledge of the skilled artisan. *Id.* at *7–8.

Salix first challenges the district court's conclusion of obviousness by asserting that *Grunenthal GMBH v. Alkem Laboratories Ltd.*, 919 F.3d 1333 (Fed. Cir. 2019) and *Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022) compel the opposite result. Appellants' Br. at 49–51. Salix further contends that the court "applied the wrong test" by not following a rationale provided in the district court opinion from *Pharmacyclics*. *Id.* at 55–57. We disagree.

In *Grunenthal*, we held that it was not clear error for the district court to find that the record failed to establish by clear and convincing evidence a reasonable expectation of success in preparing the claimed polymorphic Form A of tapentadol hydrochloride. *See* 919 F.3d at 1341. In that case, the synthesis of tapentadol hydrochloride known in the prior art produced a particular form—Form B. *Id.* The district court found that there was a lack of evidence that a prior art synthesis would have resulted in the claimed Form A and that no prior art guidance existed to establish "what particular solvents, temperatures, agitation rates, etc., were likely to result" in the claimed polymorph. *Id.* at 1343. We found no clear error in that analysis. *Id.* at 1344–45.

We also affirmed a conclusion of non-obviousness of a claimed polymorph in our non-precedential *Pharmacyclics* decision, which issued after the district court released its decision in this case. *See* 2022 WL 16943006, at *10–11. But the court here acted within its discretion when it declined to follow the district court decision in *Pharmacyclics* as though it was binding precedent. *See Decision* at *7 n.1 ("Plaintiffs call to my attention [the district court's decision in] *Pharmacyclics LLC v. Alvogen Pine Brook LLC*. I have considered that case but I do not agree with it on this point."). And our later affirmance of the factual findings in *Pharmacyclics* did not retroactively override the district court's analysis here.

Moreover, a lack of clear error in *Grunenthal* and *Pharmacyclics* does not compel a conclusion of non-obviousness here. Indeed, *Grunenthal* underscored the factual nature of these types of inquiries and expressly held that it did "not rule out the possibility that polymorph patents could be found obvious." 919 F.3d at 1344–45. "The determination of obviousness is dependent on the facts of each case." *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1089 (Fed. Cir. 2008); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007). In *Grunenthal* and *Pharmacyclics*, the issue was whether a skilled artisan would have had a reasonable expectation of success in *producing* a crystalline form of a compound. *See* 919 F.3d at 1341–43; 2022 WL 16943006, at *10–11. Here, the prior art included a process to produce a crystalline form of rifaximin, and the dispute centered around *characterizing* the crystalline form resulting from that process. *See Decision* at *13–14. These distinct factual predicates support the district courts' factual findings in each of these three cases under the clear error standard of review.

In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), the Supreme Court set forth the background against which obviousness is to be assessed: "Under § 103, the scope and content of the prior art are to be determined"

and "differences between the prior art and the claims at issue are to be ascertained." *Id.* at 17. The scope and content of the prior art here includes preparations of crystalline rifaximin, which expert testimony supports would have yielded the ß form of rifaximin. *Decision* at *7; J.A. 3391–92 ("[T]he as-synthesized form of rifaximin reported by Examples 1, 6, 7, and 9 [of Cannata] were necessarily rifaximin form Beta, because of the methods used, the solvent system used, and it was later confirmed by later work, including work from the named inventors."); *id.* at 3408–09 (similar testimony); *id.* at 3393–3404 (discussing the evidence of record that supports that conclusion); *id.* at 4700–07, 4846–47, 5007–14 (providing supporting evidence for that conclusion). And the parties do not dispute that the methods for characterizing the resulting crystalline rifaximin were well known and readily available to the skilled artisan. *Decision* at *3. The difference between the prior art and the claims is thus effectively nothing more than the performance of routine characterization to identify the polymorphic forms that result from the known Cannata processes.

In this regard, Salix does not appear to dispute that there would have been a motivation to explore potential polymorphic forms of rifaximin. Appellants' Br. at 48–49. Rifaximin was, after all, a known compound with a known, useful activity. Salix further refers to the district court's finding that "polymorph ß is a commonly produced polymorph and the most stable form of rifaximin" as an "undisputed" fact. *Id.*; *see also Decision* at *7. There thus appears to be no dispute that the claimed polymorph can be readily produced from the crystallization conditions disclosed in Cannata and that it would have been well within the abilities of the skilled artisan to procure and characterize the ß form of rifaximin.

According to Salix, however, rifaximin's ß form constituted a non-obvious invention because, although skilled artisans "actually succeed[ed]" in producing and

characterizing it, they would not have "*expect*[*ed*] to succeed" because, as of the critical date, the polymorphic nature of rifaximin had not yet been reported and the identity of the ß form remained undisclosed. Appellants' Br. at 49. Salix further argues that there could have been no expectation of success because the skilled artisan would not have been able to predict what polymorphic forms might result from following the preparation protocols disclosed in the prior art. *Id.* at 20–21, 50–53. Salix's framing of the issue suggests that no unknown entity could ever be obvious, as one cannot reasonably expect what was hitherto unknown, which is incorrect.

Here, the district court found a reasonable expectation of success in characterizing the crystalline product of Cannata for potential polymorphism using routine, conventional methods and skill. *Decision* at *6–7. We see no clear error in that conclusion. Indeed, Salix has done no more than combine known elements of the prior art to verify readily accessible information concerning a compound already in the hands of those of ordinary skill in the art, and such routine efforts do not justify removing this polymorph from the public domain. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007); *see also Pfizer*, 480 F.3d at 1367–68. To be sure, we do not hold that there is always a reasonable expectation of success in accessing or characterizing polymorphs. We are simply reviewing the district court's decision before us as to its factual finding of a reasonable expectation of success, and in so doing, have not been left with a definite and firm conviction that a mistake was made in reaching that finding. *See Scanner Techs. Corp. v. ICOS Vision Sys. Corp. N.V.*, 528 F.3d 1365, 1374 (Fed. Cir. 2008).

Having found no clear error in the district court's fact findings as to the existence of a reasonable expectation of success, we affirm the court's conclusion that the polymorph patent claims were invalid as obvious. Because we affirm the court's holding that the polymorph patent claims

would have been obvious over the asserted prior art, we need not consider Norwich's separate argument that the polymorph claims would have also been invalid as inherently anticipated.

III

On cross-appeal, Norwich raises two related but distinct arguments that arose after the district court held that Norwich infringed the HE patents and failed to establish invalidity. *See Decision* at *10–16. Norwich first argues that, in issuing its final decision, the district court misinterpreted 35 U.S.C. § 271(e)(4)(A), which directs a court, following a finding of infringement, to order the FDA to defer final approval of an ANDA until the expiration of the infringed patent. According to Norwich, that statute precludes delaying final approval of an entire ANDA, and instead requires delaying only the approval of the infringing use.

Norwich's second argument arises from its decision to amend its ANDA to carve out the infringing HE use after final judgment. Following that amendment, Norwich filed a motion to modify the final judgment to allow for prompt approval of the amended ANDA that purportedly no longer sought approval for the infringing HE use. The district court denied that motion, and Norwich cross-appealed.

We address both of Norwich's concerns in turn.

A.

We first address Norwich's arguments regarding the district court's interpretation of 35 U.S.C. § 271(e)(4)(A) in ordering that a final approval of Norwich's ANDA could not be effective before the HE patents expired. J.A. 50–51.

We review issues of statutory interpretation without deference to the district court's interpretation. *Waymark Corp. v. Porta Sys. Corp.*, 245 F.3d 1364, 1366 (Fed. Cir. 2001). "The starting point in every case involving

construction of a statute is the language itself." *Blue Chip Stamps v. Manor Drug Stores*, 421 U.S. 723, 756 (1975) (Powell, J., concurring). Moreover, we "give effect, if possible, to every clause and word of [the] statute." *United States v. Menasche*, 348 U.S. 528, 538–39 (1955) (citation omitted). When a statute does not define a given word or phrase, we presume that Congress intended the word or phrase to have its ordinary meaning. *Asgrow Seed Co. v. Winterboer*, 513 U.S. 179, 187 (1995). However, "[i]n expounding a statute, we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law, and to its object and policy." *U.S. Nat'l Bank of Or. v. Indep. Ins. Agents of Am., Inc.*, 508 U.S. 439, 455 (1993) (citation omitted).

Section 271(e)(4)(A) instructs that, following a finding of infringement, "the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." The order here instructed the FDA that "the effective date of any final approval . . . of Norwich's ANDA No. 214369 is to be a date not earlier than the date of expiration of the last to expire of [the HE patents] (currently October 2, 2029)." J.A. 51.

Norwich argues that the language of § 271(e)(4) requires courts to tie the restriction on FDA approval to the *indication* for which the ANDA seeks approval when that indication was the source of infringement. Cross-Appellants' Br. at 14. Norwich's ANDA originally sought approval for the treatment of both IBS-D and HE. Although only the HE indication was found to infringe a valid patent, the order restricted final approval of the entire ANDA, including the non-infringing indication, until 2029. Norwich argues that the statute requires the district court's order "to specify that the approval date pertains to Norwich's ANDA seeking approval for the infringing HE Indication." *Id.* at 18. But the district court order concerned only the

specific ANDA in question that included an infringing use, referred to the ANDA by its number, and enjoined the approval of that ANDA. J.A. 51. Norwich suggests that the district court order unfairly precludes it from receiving final approval of a new non-infringing ANDA.[10] The district court did no such thing.

Section 271(e)(4)(A) describes delaying the approval of "the drug . . . involved in the infringement." Since the FDA does not approve drugs in the abstract, but rather approves drugs for particular uses (indications) of that drug, the statute is appropriately construed as directed to approval of particular infringing uses of the drug, not all uses of the drug including non-infringing uses. The statutory scheme makes clear that it is not the potential use of Norwich's rifaximin for HE that constitutes the relevant infringement here, nor is it the unpatented drug compound itself, but rather it is the submission of the ANDA that included an infringing use. *See* 35 U.S.C. § 271(e)(2)(A) (making it an "act of infringement to submit" an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent"). That the ANDA further recited a non-patent-protected indication does not negate the infringement resulting from the ANDA's submission. The order thus appropriately delayed the effective final approval date of "this infringing ANDA" submission. J.A. 48. The order appropriately said nothing that would prevent approval of a new non-infringing ANDA.

We therefore affirm the district court's order setting the effective approval date of Norwich's ANDA No. 214369

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[10] Norwich notes that on June 2, 2023, FDA tentatively approved its amended ANDA, which purportedly lacks the HE indication. Cross-Appellant's Br. at 6. The tentative approval letter noted, however, that "final approval cannot be granted until October 2, 2029 as specified in the court order." *Id.*

to be no earlier than the date of expiration of the last to expire of the HE patents.

B.

Following entry of the final judgment, which included the resetting order barring final approval of Norwich's ANDA until 2029, Norwich amended its ANDA in an attempt to remove the infringing HE indication. Norwich then moved to modify the judgment under Federal Rule of Civil Procedure 60(b), asserting that the amendment negated any possible infringement, and that the final approval date of the ANDA, as amended, should not be tied to the HE patents. *See* Cross-Appellant's Br. at 27. The district court denied that motion, holding that Norwich "fully litigated the merits of its non-infringement and invalidity case, lost, and now seeks a way around the final judgment through Rule 60(b)." *Rule 60(b) Order* at *2. Norwich cross-appealed.

"Because denial of a Rule 60(b) motion is a procedural issue not unique to patent law, we apply the rule of the regional circuit where appeals from the district court would normally lie," *Amstar Corp. v. Envirotech Corp.*, 823 F.2d 1538, 1550 (Fed. Cir. 1987), which, here, is the Third Circuit. The Third Circuit "review[s] the denial of Rule 60(b) relief for an abuse of discretion." *Coltec Indus., Inc. v. Hobgood*, 280 F.3d 262, 269 (3d Cir. 2002); *see also Bohus v. Beloff*, 950 F.2d 919, 930 (3d Cir. 1991) (noting that Rule 60(b) motions are "extraordinary relief which should be granted only where extraordinary justifying circumstances are present" (citation omitted)).

"A district court may reconsider its own finding of infringement in light of an amended ANDA," but the court need not do so. *Ferring B.V. v. Watson Lab'ys, Inc. Fla.*, 764 F.3d 1382, 1391 (Fed. Cir. 2014). Rather, "[a]llowing an amendment is within the discretion of the district court, guided by principles of fairness and prejudice to the patentholder." *Id.* Here, the court reasonably held that

consideration of the amended ANDA would be inequitable and inappropriate. *Rule 60(b) Order* at *2. The court noted that "[i]t is not a simple matter to determine whether an ANDA applicant has successfully carved out language from a label to turn infringement into non-infringement" and that what Norwich sought in its Rule 60(b) motion "would essentially be a second litigation" following final judgment. *Id.* (noting also that, other than simply asserting that it carved out the HE indication and providing the court with the amended label, Norwich "ha[d] presented no evidence in support of its assertion" that the amended ANDA would no longer infringe the HE patents).

Norwich nevertheless argues that the amended ANDA satisfies the judgment by not seeking approval for the infringing use and that, in view of the amendment, it is no longer equitable to apply the judgment prospectively. But Rule 60(b) is permissive, holding only that the court "*may* relieve a party or its legal representative from a final judgment, order, or proceeding" under various circumstances. That is—a district court has the discretion, not the obligation, to modify a final judgment in view of a post-judgment ANDA amendment. And as the district court held, simply asserting that a patented indication has been carved out of an ANDA application does not necessarily satisfy the judgment or entitle the applicant to direct entry to the market. *See Rule 60(b) Order* at *2. We see no abuse of discretion in the district court reaching that conclusion or in subsequently denying the motion.

Norwich further argues that the district court erred by not explicitly discussing Rule 60(b)(6), which provides that a court may relieve a party from a final judgment for "any other reason that justifies relief." We disagree that the district court so erred. The court's Memorandum Order thoroughly discussed the law, the equities, the record, and the arguments before it. In so doing, the court implicitly found no additional reason that justified the relief that Norwich sought.

We therefore affirm the district court's denial of the motion to modify the final judgment.

CONCLUSION

We have considered both parties remaining arguments and find them unpersuasive. For the foregoing reasons, we affirm (1) the district court's holding that claim 2 of the '569 patent, claim 3 of the '667 patent, claim 4 of the '199 patent, and claim 36 of the '206 patent would have been invalid as obvious, (2) the district court's order setting the effective approval date of Norwich's ANDA to be no earlier than the date of expiration of the last to expire of the HE patents, and (3) the district court's denial of the motion to modify the final judgment.

AFFIRMED

COSTS

No costs.

United States Court of Appeals for the Federal Circuit

SALIX PHARMACEUTICALS, LTD., SALIX PHARMACEUTICALS, INC., BAUSCH HEALTH IRELAND LTD., ALFASIGMA S.P.A.,
Plaintiffs-Appellants

v.

NORWICH PHARMACEUTICALS INC.,
Defendant-Cross-Appellant

2022-2153, 2023-1952

Appeals from the United States District Court for the District of Delaware in No. 1:20-cv-00430-RGA, Judge Richard G. Andrews.

CUNNINGHAM, *Circuit Judge*, dissenting in part.

I join most of the majority's opinion, but I respectfully dissent from the majority's opinion concerning U.S. Patent Nos. 8,309,569 and 10,765,667 (the "IBS-D patents"). I would vacate the district court's judgment that the asserted claims of the IBS-D patents are obvious and remand for further proceedings.

I

The district court found that "[t]he asserted IBS-D claims describe a dosing regimen within the known range" and that "[a] POSA would have been motivated to combine

the RFIB 2001 Protocol[1] and Pimentel 2006[2] with a reasonable expectation of success." *Salix Pharms., Ltd. v. Norwich Pharms., Inc.,* No. 20-430-RGA, 2022 WL 3225381, at *17 (D. Del. Aug. 10, 2022) ("*Decision*") (footnotes added). Based on these findings of fact, the court concluded that "Pimentel 2006 in light of the RFIB 2001 Protocol renders the asserted claims of the IBS-D patents obvious." *Id.* at *18. After reviewing the evidence relied on by the district court, applying a clear error standard, I am "left with the definite and firm conviction that a mistake has been committed" regarding these findings. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1359 (Fed. Cir. 2007) (quoting *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948)).

The evidence cited by the district court does not support its finding that a skilled artisan would have a reasonable expectation of success for the claimed dosage. *See Decision* at *17, *19. "The reasonable-expectation-of-success analysis must be tied to the scope of the claimed invention"—here, the claimed 1,650 mg/day (550 mg TID[3]) dosage for treating IBS-D. *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021). The district court mainly relied on the results of the

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[1] ClinicalTrials.gov, *History of Changes for Study: NCT00269412, Randomized, Double Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Three Different Doses of Rifaximin Administered BID Either Two or Four Weeks in the Treatment of Patients with Diarrhea-Associated Irritable Bowel Syndrome* (December 22, 2005); J.A. 7048–55.

[2] M. Pimentel et al., *The Effect of a Nonabsorbed Oral Antibiotic (Rifaximin) on the Symptoms of the Irritable Bowel Syndrome*, 145 ANNALS INTERN. MED. 557 (2006); J.A. 4639–46. The majority refers to this reference as Pimentel.

[3] TID stands for three times per day.

RFIB 2001 trial disclosed in the RFIB 2001 Press Release[4] in arriving at this conclusion. *Decision* at *19. However, there is no reason that a skilled artisan "would have known about the successful RFIB 2001 Protocol results," *id.*, as to the claimed 1,650 mg/day (550 mg TID) dosage because the RFIB 2001 Press Release only discloses an improvement in the *550 mg twice-a-day* group. J.A. 7480; *see Decision* at *19. In fact, evidence in the record suggests the opposite—that a skilled artisan might have understood the absence of discussions of the *1,100 mg twice-a-day* group to imply that higher dosage *did not* lead to similar successful results. *See* J.A. 3313–14. Indeed, the 2,200 mg/day dosage "did not achieve more responders compared to the placebo for adequate relief."[5] J.A. 3042. Thus, the court's reliance on the RFIB 2001 Press Release to establish a reasonable expectation of success was erroneous.[6]

The district court's citations to other references do not cure this error. Cuoco[7] discloses a total dose of *1,200*

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[4] Salix Pharms., Ltd., Current Report (Form 8-K) (Sept. 5, 2007); J.A. 7477–82.

[5] Although the evidence that the 2,200 mg/day dosage did not achieve adequate relief post-dates the priority date of the patent, it clarifies what a skilled artisan would have understood from the RFIB 2001 Press Release. *See Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1379 (Fed. Cir. 2005) (holding district court erred in not considering a reference that post-dates the priority date when it is relevant to what "was known in the art at the relevant time").

[6] Salix also challenges the district court's finding that the RFIB 2001 Press Release was prior art. Appellant's Br. 30–39; *Decision* at *20. I agree with the majority that we do not need to reach this issue.

[7] L. Cuoco & M. Salvagnini, *Small intestine bacterial overgrowth in irritable bowel syndrome: a retrospective*

mg/day for 14 days, and Barrett[8] similarly discloses 400 mg TID for a total dosage of *1,200 mg/day*. *Decision* at *19; *see also* J.A. 4536; J.A. 4800. The district court did not explain why these references would give rise to a reasonable expectation of success for a dosage that is almost 40% higher. The reference by the district court to the "[w]idespread off-label use" of rifaximin was also unaccompanied by any discussion of dosages or citations to the record. *Decision* at *19. Likewise, it discussed market research that shows many physicians prescribe rifaximin for IBS without discussing their prescribed dosages. *Decision* at *20 (citing J.A. 7186). The cited research does not show that physicians prescribe at the 1,650 mg/day (550 mg/TID) dosage. J.A. 7186.

Although "efficacy data is [not] always required for a reasonable expectation of success," *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019), the analysis must still be tied to the scope of the claims—here, the 1,650 mg/day dosage. *See Teva*, 18 F.4th at 1381; *see also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1070–72 (Fed. Cir. 2012) (finding no reasonable expectation of success when the court "cited no evidence specifically indicating that a [drug with a pK profile disclosed in the prior art] would be expected to yield the same therapeutic effect as [a different pK profile as claimed]"); *Ferring B.V. v. Watson Lab'ys, Inc.-Fla.*, 764 F.3d 1401, 1407 (Fed. Cir. 2014) (finding asserted claims not to be invalid for obviousness when prior art references "disclose 500 mg [] formulations, but no

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study with rifaximin, 52 MINERVA GASTROENTEROL. DIETOL. 89 (2006); J.A. 4533–39.

[8] G. Barrett, Abstract, *Benefits of the Antibiotic Rifaximin as Empiric Therapy in Patients with Irritable Bowel Syndrome*, 101 AM. J. GASTROENTEROL. S479 (2006); J.A. 4799–4800.

higher tablet strengths, and particularly not the claimed 650 mg formulation"). Aside from its erroneous reliance on the RFIB 2001 Press Release, the district court failed to tie its reasonable expectation of success analysis to the claimed dosage. Therefore, I would find that it clearly erred in its reasonable expectation of success analysis.

In sum, the district court clearly erred in relying on the RFIB 2001 Press Release and other references that do not teach the claimed dosage. For these reasons, I would have found the district court's finding to be clearly erroneous and would vacate the district court's judgment that the IBS-D claims were invalid as obvious.

II

In affirming the district court's judgment of obviousness, the majority relies on one additional sentence in Pimentel 2006 regarding the reasonable expectation of success analysis: "Recent data suggest that the optimal dosage of rifaximin may, in fact, be higher than that used in our study." J.A. 4644; *see* Maj. Op. 8. But the lack of discussion of any actual dosage that may be optimal, the use of the word "may," and the fact that the RFIB 2001 Protocol discloses a specific dosing regimen of 2,200 mg/day rather than 1,650 mg/day all call into question the majority's finding. Indeed, the district court only relied on this sentence in its motivation to combine analysis and did not rely on this sentence in its reasonable expectation of success analysis. *See Decision* at *18–20. The parties never made this argument before us. Therefore, I disagree that this additional sentence, when considered together with the RFIB 2001 Protocol, would give rise to a reasonable expectation of success for the claimed dosage.

The majority also discusses references not relied on by the district court in its reasonable expectation of success

analysis, including Lauritano[9], Scarpellini[10], and Lin.[11] Maj. Op. 9–10. But the district court did not make any findings on what these references teach, other than finding that the references were prior art. *See Decision* at *17–22. Nor are the majority's conclusions regarding these references uncontested. For example, Salix argues that Scarpellini and Lauritano are both directed to the treatment of small intestinal bacterial overgrowth (SIBO), not to the treatment of IBS or IBS-D, and therefore cannot establish a reasonable expectation of success. Appellant's Reply Br. 18. Although the majority may be right that Lauritano's and Scarpellini's disclosures on treating SIBO also support finding a reasonable expectation of success for treating IBS-D, *see* Maj. Op. 9–10, the district court never made this finding. *See Golden Bridge Tech., Inc. v. Nokia, Inc.*, 527 F.3d 1318, 1323 (Fed. Cir. 2008) (declining to find what a prior art reference teaches in the first instance). It merely found that "[t]he relationship between IBS and SIBO was actively being explored," and that certain prior art references "do not teach away from using rifaximin to treat IBS." *Decision* at *21. I would not make such fact-findings about Scarpellini and Lauritano in the first instance.

In summary, I would vacate the district court's judgment that the asserted claims of the IBS-D patents were obvious and remand for further proceedings. On remand, I would order the district court to consider in the first instance the teachings in the additional prior art references.

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[9] E.C. Lauritano et al., *Rifaximin dose-finding study for the treatment of small intestinal bacterial overgrowth*, 22 ALIMENT. PHARMACOL. THER. 31 (2005); J.A. 7267–71.

[10] E. Scarpellini et al., *High dosage rifaximin for the treatment of small intestinal bacterial overgrowth*, 25 ALIMENT. PHARMACOL. THER. 781 (2007); J.A. 4663–67.

[11] International Patent Application Publication No. WO 2006/102536; J.A. 4721–47.

See ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 1578 (Fed. Cir. 1984) ("Where the trial court fails to make findings, the judgment will normally be vacated and the action remanded for appropriate findings to be made."). Accordingly, I respectfully dissent in part.