APPENDIX

APPENDIX

TABLE OF CONTENTS

APPENDIX A

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

WILLIAM R. PETERSON, Morgan, Lewis & Bockius LLP, Houston, TX, argued for plaintiffs-appellants. Also represented by MICHAEL J. ABERNATHY, KARON NICOLE FOWLER, MICHAEL SIKORA, Chicago, IL; JULIE S. GOLDEMBERG, Philadelphia, PA; JOSHUA DANIEL CALABRO, SHANNON KEOUGH CLARK, STEVEN C. KLINE, ALEXIS M. MCJOYNT, SCOTT K. REED, BECKY E. STEEPHENSON, Venable LLP, New York, NY.

CHAD A. LANDMON, Axinn, Veltrop & Harkrider LLP, Hartford, CT, argued for defendant-cross-appellant. Also represented by MATTHEW BECKER, REBECCA L. CLEGG, THOMAS K. HEDEMANN, MATTHEW S. MURPHY.

IRENA ROYZMAN, Kramer Levin Naftalis & Frankel LLP, New York, NY, for amici curiae Regeneron Pharmaceuticals, Inc., Ocular Therapeutix, Inc. Also represented by CHRISTINE WILLGOOS; PAUL BRZYSKI, Washington, DC.

PAUL WHITFIELD HUGHES, III, McDermott Will & Emery LLP, Washington, DC, for amicus curiae Vanda Pharmaceuticals Inc. Also represented by CHRISTOPHER MICHAEL BRUNO, SARAH HOGARTH, APRIL ELISE WEISBRUCH.

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 β ("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

---

[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*

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 *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.

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.

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

---

[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").

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 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

---

[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.

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

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 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 Ex-

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

change 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.

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 β 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.

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

---

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

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

---

[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*.

No. 214369 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 patent-holder." *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

---

[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.

F.4th 1377, 1381 (Fed. Cir. 2021). The district court mainly relied on the results of the 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]

---

[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.

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

---

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

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 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*

---

[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.

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. *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.

APPENDIX B

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE

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

v.

NORWICH PHARMACEUTICALS, INC.,
Defendant.

Civil Action No. 20-430-RGA

Filed: August 10, 2022

TRIAL OPINION

Jack B. Blumenfeld, Karen Jacobs, Cameron P. Clark, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, Wilmington, DE; Scott K. Reed, Steven C. Kline, Shannon K. Clark, Daniel A. Apgar, Alexis M. McJoynt, Damien N. Dombrowski, Becky E. Steephenson, VENABLE LLP, New York, NY.

Attorneys for Plaintiffs.

Karen E. Keller, Nathan R. Hoeschen, SHAW KELLER LLP, Wilmington, DE; Matthew J. Becker, Stacie L.

Ropka, Matthew S. Murphy, Chad A. Landmon, Rebecca L. Clegg, AXINN, VELTROP & HARKRIDER LLP, Hartford, CT; Aziz Burgy, AXINN, VELTROP & HARKRIDER LLP, Washington, DC; Richardo S. Camposanto, AXINN, VELTROP & HARKRIDER LLP, San Francisco, CA.

Attorneys for Defendant.

August 10, 2022

/s/ RICHARD G. ANDREWS
ANDREWS, U.S. DISTRICT JUDGE:

Salix sued Norwich for infringement of twenty-six patents that cover Salix's branded Xifaxan (rifaximin) 550 mg tablets. (D.I. 59 ¶¶ 12, 41). Before trial, Salix narrowed its case to U.S. Patent Nos. 7,612,199, 7,902,206 ("the Polymorph Patents"), 8,642,573, 9,421,195, 10,335,397 ("the HE Patents"), 8,309,569, and 10,765,667 ("the IBS-D Patents"). In March 2022, I held a four-day bench trial. (D.I. 168-172, hereinafter "Tr.").

I. BACKGROUND

Norwich submitted an Abbreviated New Drug Application (ANDA) to the Food and Drug Administration (FDA) for approval to market a generic version of Xifaxan. Salix alleges infringement under § 271(e)(2)(A) of the Patent Act. 35 U.S.C. §271(e)(2)(A). Norwich counters that the asserted patents are invalid.

In 2004, the FDA approved Xifaxan (rifaximin) 200 mg tablets to treat travelers' diarrhea. (D.I. 155 ¶ 9). On March 24, 2010, the FDA approved Xifaxan

(rifaximin) 550 mg tablets to reduce the risk of overt hepatic encephalopathy ("HE") recurrence in adults. (*Id.* ¶10). On May 27, 2015, the 550 mg tablets were approved to treat irritable bowel syndrome with diarrhea ("IBS-D") in adults. (*Id.* ¶11). The asserted patents cover a polymorphic form of rifaximin and methods of treating HE and IBS-D in adults.

II. LEGAL STANDARD

A. Infringement

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent . . . ." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Under § 271(b), whoever actively induces infringement of a patent shall be liable as an infringer." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). To prevail on a theory of induced infringement, a plaintiff must prove (1) direct infringement and (2) "that the defendant possessed specific intent to encourage another's infringement and not merely that the defendant had knowledge of the acts alleged to constitute infringement." *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d

1117, 1129 (Fed. Cir. 2019) (quoting *DSU Med. Corp. v. JMA Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006)).

In a Hatch-Waxman case, a plaintiff "can satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the [asserted patent]." *Vanda*, 887 F.3d at 1130. For method-of-treatment patents, if an ANDA applicant's "proposed label instructs users to perform the patented method . . . , the proposed label may provide evidence of [the ANDA applicant's] affirmative intent to induce infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). "When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, the label must encourage, recommend, or promote infringement." *Vanda*, 887 F.3d at 1129 (cleaned up).

B. Obviousness

A patent is invalid as obvious under 35 U.S.C. § 103 if "the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made." *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479 (Fed. Cir. 1998). "Obviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness." *In re Morsa*, 713 F.3d 104, 109 (Fed. Cir. 2013) (citations omitted).

To show a patent is obvious, a party "must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the

teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014) (cleaned up). The overall inquiry into obviousness, though, must be "expansive and flexible." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415 (2007). In conducting the obviousness analysis, "a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

C. Written Description

The written description "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed.Cir.2010) (en banc) (cleaned up). The test is whether the disclosure "conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* This requires an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.*

D. Indefiniteness

35 U.S.C. § 112 requires that claims "particularly point[] out and distinctly claim[] the subject matter." The claims, viewed in light of the specification and prosecution history, must "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments*, Inc., 572 U.S. 898, 910 (2014). "While a claim employing a term of degree may be definite where it provides enough certainty to one of skill in the art when read

in the context of the invention, a term of degree that is purely subjective and depends on the unpredictable vagaries of any one person's opinion is indefinite." *Intell. Ventures I LLC v. T-Mobile USA, Inc.*, 902 F.3d 1372, 1381 (Fed. Cir. 2018) (cleaned up).

III. THE POLYMORPH PATENTS

The Polymorph Patents claim polymorphic forms of rifaximin. Plaintiffs assert two such claims. Asserted Claim 4 of the '199 patent states:

> 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%.

Asserted Claim 36 of the '206 patent depends on claim 34:

> 34. A solid pharmaceutical composition comprising rifaximin in polymorphic Form ß and a pharmaceutically acceptable excipient or carrier, wherein the rifaximin Form ß has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 2-θ.
>
> 36. The pharmaceutical composition of claim 34, wherein the rifaximin Form ß has a water content of between about 4.5% to about 40%.

A. Findings of Fact

1. If approved, Norwich's ANDA product will infringe the asserted claims of the Polymorph Patents.

2. The priority date of the asserted polymorph claims is November 7, 2003.

3. A person of skill in the art (a "POSA") would have had a B.S. in chemistry, chemical engineering, or a related discipline with at least 3 years' experience in the pharmaceutical industry related to API manufacturing, crystallization, characterization, or evaluation of solid state forms. Or a POSA would have had an advanced degree with less or no experience.

4. The '199 patent is a continuation of, and contains substantially the same disclosures as, the '206 patent.

5. Rifaximin exists in polymorphic forms. Norwich's ANDA product comprises polymorphic form β.

6. X-ray powder diffraction (XRPD) peaks are an inherent characteristic of a polymorph. Each peak in an XRPD diffractogram is a structural element of that form. XRPD was routine as of the priority date.

7. A crystalline form of a known compound can be characterized by a subset of XRPD peaks. The subset of XRPD peaks at about 5.4°, 9.0°, and 20.9° 2θ was sufficient as of the priority date to distinguish rifaximin β from the other known rifaximin polymorphs.

8. Water content is an inherent characteristic of a crystal form that can be determined by routine testing methods such as Karl Fischer (KF) or thermogravimetric analysis (TGA).

9. Cannata, Marchi, and the Normix Label are prior art.

10. Cannata disclosed crystalline rifaximin, methods of making it, and that it had antibacterial properties.

11. The four post-filing references relied upon by Defendant's expert, Dr. Zaworotko, do not show that any of the Cannata methods produces rifaximin ß every time.

12. Cannata does not inherently anticipate the asserted polymorph claims.

13. Marchi disclosed methods of preparing crystalline rifaximin, rifaximin's antibacterial properties, and that it could be used in pharmaceutical compositions with conventional pharmaceutically acceptable excipients or carriers.

14. The Normix Label describes the use of rifaximin as a pharmaceutical.

15. Cannata in view of common knowledge discloses each and every limitation of claim 4 of the '199 patent.

16. A POSA would have had a motivation to combine Cannata with commonly known testing techniques XRPD and KF or TGA because regulatory bodies instructed applicants to characterize the solubility, stability, and bioavailability of drug candidates.

17. A POSA would have had a reasonable expectation of success at characterizing the rifaximin ß polymorph and arriving at the claimed XRPD peaks at

about 5.4°, 9.0°, and 20.9° 2θ and water content of greater than 5%.

18. Marchi in view of Cannata and common knowledge discloses each and every limitation of claim 36 of the '206 patent.

19. A POSA would have had a motivation to combine Cannata with Marchi in light of common knowledge.

20. A POSA would have had a reasonable expectation of success at achieving a pharmaceutical composition comprising rifaximin β and a pharmaceutically acceptable excipient or carrier.

21. All rifaximin β claim limitations are expressly disclosed in the specifications of the Polymorph Patents.

B. Infringement

Norwich admits that its ANDA Product, if approved, will infringe claim 4 of the '199 patent and claim 36 of the '206 patent. (D.I. 148, Ex. 1, ¶¶ 126, 127).

C. Invalidity

1. Inherent Anticipation

Each expert asserts that his validity analysis is not impacted by which definition of a POSA I use. (Tr. 860:7-861:8; Tr. 936:21-937:13). In view of Defendant's burden to prove invalidity by clear and convincing evidence, I will adopt Plaintiffs' definition of a POSA.

Norwich argues that U.S. Patent No. 4,557,866 (the "Cannata" reference) (JTX-37) inherently anticipates claim 4 of the '199 patent because it discloses a process that necessarily produces the claimed rifaximin ß. (D.I. 176 at 32). "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). A disclosed process may anticipate "if it discloses in an enabling manner the production" of the claimed polymorph. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1344 (Fed. Cir. 2005).

Here, the issue is whether the process disclosed by Cannata invariably produces rifaximin ß. Norwich has presented the following evidence in support:

- The "Viscomi Declaration," a declaration to the PTO stating that samples of batches produced according to Cannata "are composed either of mixture of polymorph (alpha and beta, and in some case alpha and epsilon) or different polymorphs." (JTX 80 ¶ 7).
- The "Viscomi 2008" article, which Norwich's expert Dr. Zaworotko testified shows that rifaximin ß is a necessary precursor to the formation of rifaximin α, δ, and ε. (JTX 65; Tr. 880:20-881:1, 921:24-922:6).
- The "Braga 2012" article, which describes the inherent properties of rifaximin ß. (JTX 105).

- The "Bacchi 2008" article, which described rifaximin beta 4 ("RX4"), a substance the author concluded was "the so-called beta rifaximin of the literature." (DTX 43; Tr. 882:14–24). The article describes slow evaporation as the method of preparation. From this article, Dr. Zaworotko concluded, "Examples 1 and 7, at the very least, of Cannata would have . . . necessarily afforded rifaximin Beta because of the solvent system used, the method used of controlled crystallization, and the lack of drying or lack of aggressive drying." (Tr. 883:6–10).

According to this evidence, Norwich argues, "Cannata inherently produced rifaximin ß every time, either directly *or as a necessary precursor* to the α, δ, and ε forms and mixtures disclosed in the Viscomi Declaration." (D.I. 185 at 9).

I do not think this evidence amounts to clear and convincing evidence that Claim 4 is inherently anticipated by Cannata. Norwich could have shown anticipation either because (1) as a law of nature, rifaximin α, δ, and ε cannot exist without having been derived from rifaximin ß, or (2) a method disclosed in Cannata produces rifaximin ß each and every time it is practiced. Dr. Zaworotko's testimony did not prove either.

Dr. Zaworotko's opinion does not clearly support the conclusion that, as a law of nature, rifaximin ß is a necessary precursor to rifaximin α, δ, and ε. For one thing, had that been his opinion, he could have clearly stated that, and I do not think he did. (*See* Tr. at 870-884). I think Dr. Zaworotko's opinion was relying upon the Viscomi 2008 article:

> Q: Would rifaximin Beta form as a precursor to any polymorph listed in the Viscomi declaration listed at paragraph 7?
>
> A: Yes, based upon the Viscomi 2008 article, where the effect of moisture on rifaximin crystal forms was studied and based upon the diagram [derived from Viscomi 2008] it's clear that Beta has to be the precursor for any of the other crystal forms with lower water content.

(Tr. 921:25–922:1). This opinion appears to be based on Dr. Zaworotko's reading of Viscomi 2008, and not a conclusion that rifaximin α, δ, and ε cannot exist in the world without having first been rifaximin ß. I think Dr. Zaworotko stated his opinion the way he did because the "diagram" to which Dr. Zawortko refers, which is based on Figure 4 ("The relationship between the various crystal forms of rifaximin"), was not the main point of the article. The article's purpose, consistent with its title ("Crystal forms of rifaximin and their effect on pharmaceutical properties") was to report on a "study [] to identify the presence of crystal forms of rifaximin and to assess their impact on parameters such as solubility, intrinsic dissolution and bioavailability." (JTX-65 at 1074). The paper concluded, "The unexpected outcome of this study is that we have found that some crystal forms of rifaximin are significantly absorbed, while it was previously considered a non-absorbable drug. These finding[s] indicate the need of putting appropriate manufacturing and analytical procedures in place to consistently yield rifaximin of the appropriate crystalline structure." (*Id.* at 1080). Thus, to the extent Dr. Zaworotko was offering an opinion that Viscomi 2008 is conclusive

proof that rifaximin α, δ, and ε are necessarily derived from rifaximin β, I do not find that conclusion to be well-supported. It is not clear and convincing proof.

Thus, to show that Cannata inherently anticipates Claim 4, Norwich would need to show that every time Cannata is performed, rifaximin β is produced. Norwich has not done so.

The Viscomi Declaration does not help Norwich. It stated that among "samples of batches" produced according to Cannata, when retested in 2006, there were four batches with no rifaximin β. The four batches consisted of (1) only the "delta polymorph," (2) only of the "epsilon form," (3) a mixture of "the alpha and epsilon form," and (4) a mixture of the "alpha and delta forms," respectively. (JTX-80, ¶7; *see* Tr. 949:8-12).

Although Viscomi 2008 states that the "method of production of rifaximin" was disclosed in European Patent No. 161534, the counterpart to Cannata, Salix has persuasively argued that Viscomi 2008 discloses steps that are more specific than what Cannata describes. (*See* JTX 105 at 6404 n.3; JTX 65 at 1074 & 1074 n.29; Tr. 874:16-25).

In Viscomi 2008, the reaction step for preparing wet rifaximin describes (1) heating the reaction mixture to 50°C for 5 hours, then cooling it to 20°C; (2) adding a mixture of 0.1 moles of ascorbic acid and 2.5 moles of concentrated hydrochloric acid in 220 mL of 58% ethyl alcohol in water over 30 minutes; and (3) adding concentrated hydrochloric acid dropwise until pH 2.0 is reached. (Tr. 951:8-13; JTX 65 at 1074). Cannata has none of these details. (Tr. 951:13-17). The crystallization step in Viscomi is also described

with more precision than in Cannata. (Tr. 951:18–952:2).

Similarly, Bacchi 2008 discloses a process that does not precisely match Cannata's examples 1 and 7. Bacchi describes using a "slow evaporation" process while Cannata does not mention evaporation. (DTX 43 at 1734; Tr. 949:20-22). Furthermore, the Cannata examples crystallize rifaximin from a 7:3 ethanol to water mixture, whereas Bacchi does not disclose any ethanol to water ratio. (Tr. 949:15-23; Tr. 953:2-954:3).

Ultimately, it appears that Cannata left certain steps up to the discretion of the chemist preparing the rifaximin. To show that Cannata invariably produces rifaximin ß, Norwich would have needed to show that, no matter how the chemist exercised his or her discretion, rifaximin ß would be produced. I do not think Norwich has done so. "Experiments that do not follow the prior art procedure alleged to inherently anticipate cannot show inherent anticipation." *Merck & Cie v. Watson Lab'ys, Inc.*, 125 F. Supp. 3d 503, 513 (D. Del. 2015) (cleaned up), *rev'd on other grounds*, 822 F.3d 1347 (Fed. Cir. 2016).

Thus, I find that Norwich has not shown by clear and convincing evidence that claim 4 of the '199 patent is inherently anticipated by Cannata.

2. Obviousness

Norwich contends that claim 4 of the '199 patent is obvious over Cannata in view of common knowledge. (D.I. 176 at 34–35). Norwich contends that claim 36 of the '206 patent is obvious over Cannata in view of the Normix Label and common knowledge or

over Marchi in view of Cannata and common knowledge. (*Id.* at 35).

A POSA would have understood from Cannata that rifaximin exists in crystalline form and that rifaximin has "outstanding antibacterial properties." (JTX 37 at 3:10-16, 5:21–36). Norwich argues this knowledge would motivate a POSA to "identify the characteristics of the obtained rifaximin" using "routine methods." (D.I. 176 at 35). Furthermore, Norwich argues that a POSA would recognize "that the crystallization solvent used by Cannata included water, which could lead to hydrate formation, and thus [the POSA] would have been motivated to analyze the effect of water on the crystalline form using conventional methods." (*Id.*). A POSA could have performed a "routine humidity experiment . . . in one day and detected rifaximin ß." (*Id.*).

The Court of Appeals considered the obviousness of a polymorph patent in *Grunenthal GmbH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1336 (Fed. Cir. 2019). The *Grunenthal* patent claimed Form A of tapentadol hydrochloride characterized by its XRPD peaks. *Id.* The *Grunenthal* defendant, Alkem, argued that the claim was obvious in light of prior art that disclosed a Form B of tapentadol hydrochloride. *Id.* at 1337.

Alkem's prior art references included (1) the prior art patent that described a crystalline form of tapentadol hydrochloride (later called "Form B") and (2) an article that "outlines a number of variables that may be adjusted during the recrystallization process to determine whether polymorphism occurs in a compound." *Id.* at 1337, 1341. The "polymorphism of tapentadol hydrochloride was unknown at the time of

filing the [asserted patent]," and "Form B was the only crystal structure . . . known in the art at the time." *Id.* at 1341.

The Court of Appeals found that the article did not provide "guidelines regarding which [variables] are likely to result in polymorphs of particular compounds." *Id.* at 1342. Thus, the article did little more than tell a POSA to "vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result," which does not provide a reasonable expectation of success. *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348,1365 (Fed. Cir. 2007)).

Here, the prior art includes Cannata, which discloses processes for preparing a crystalline form of rifaximin. As in *Grunenthal*, rifaximin's polymorphism was unknown as of the priority date. In *Grunenthal*, however, the prior art patent was known to produce a particular form—Form B—of tapentadol hydrochloride. Here, by contrast, no rifaximin had been publicly characterized as a particular form as of the priority date.

I think the evidence is clear and convincing that a POSA would have been motivated to characterize the rifaximin produced by the Cannata processes. Cannata disclosed that rifaximin had strong antibacterial properties and low bioavailability, motivating a POSA to evaluate the substance as a potential drug candidate. (JTX 37 at 3:10-16; JTX 94 at 6-7; Tr. 869:16–870:4; Tr. 891:16-892:12). The FDA encouraged, if not required, that the solid forms of a drug substance be well-characterized during drug development, includ-

ing as to the properties of solubility, stability, and bioavailability. (DTX 315-35; Tr. 892:13-894:7). XRPD profiling was the predominant method for identifying crystalline materials. (DTX 315-38; Tr. 894:23-895:12). FDA guidance required "appropriate manufacturing and control procedures" when manufacturing and storing the drug substance could result in a hydrated drug substance. (DTX 315-39; Tr. 895:13–24). Because the Cannata process for preparing rifaximin used water, a POSA would know about the potential for a hydrate to form, and be motivated to perform routine testing (e.g., KF or TGA) for water content and hydration formation. (DTX 317-19; JTX 54 at 182; Tr. 888:3-890:5; DTX 315-39).

I think the evidence shows that a POSA would have a reasonable expectation of success in characterizing the polymorph ß, as opposed to the other forms of rifaximin. Although Norwich's evidence failed to show that ß was produced each and every time rifaximin was prepared according to Cannata, it did strongly suggest that polymorph ß is a commonly produced polymorph and the most stable form of rifaximin.

The Viscomi Declaration stated that rifaximin prepared according to Cannata yielded ß along with other polymorphs. (JTX 80 at ¶ 7). Dr. Zaworotko explained that ß is the most stable form. Tr. 877:17-18. ("[B]eta is the winner in terms of stability under normal conditions of temperature and humidity."). Dr. Myerson's critiques of Dr. Zaworotko's testimony do not have the same force in the context of obviousness as they did in the context of inherent anticipation. While Viscomi 2008's increased specificity in the

method of preparation suffices to suggest that Cannata may not produce rifaximin ß each and every time (as would be required for inherent anticipation), the standard for obviousness is a reasonable expectation of success. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a certainty of success.").

I reject Salix's argument that a POSA would not have been able to predict the precise peaks that characterize rifaximin ß, and accordingly a POSA would not have had a reasonable expectation of success. The Federal Circuit has held, "[A] rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt . . . would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). I think the same is true in this context. I credit the testimony of Dr. Zaworotko that the XRPD peaks and water content are "inherent" properties of a crystal form that can be tested using routine methods. (Tr. 871:20–872:5; 884:2–13; 895:8–12). Thus, a POSA would have a reasonable expectation of success at characterizing the polymorph and arriving at the claimed XRPD peaks and water contents.[1]

---

[1] Plaintiffs call to my attention *Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 412 (D. Del. 2021), *app. filed*, No. 21-2270 (Fed. Cir. Aug. 31, 2021). (D.I. 181 at 37). I have considered that case but I do not agree with it on this point.

There is no evidence of secondary considerations of nonobviousness for the Polymorph Patents. (*See* D.I. 174 at 15–18).

Thus, I find by clear and convincing evidence that claim 4 of the '199 patent is obvious in light of Cannata in view of common knowledge.

Claim 36 of the '206 patent claims a pharmaceutical composition comprising (1) rifaximin ß with the claimed XRPD peaks and a water content between about 4.5% to 40% and (2) a pharmaceutically acceptable excipient or carrier.

Norwich argues that rifaximin had previously been formulated as a pharmaceutical composition comprising pharmaceutically acceptable excipients or carriers. (D.I. 176 at 37). Marchi in 1982 and the Normix Label in 2001 each taught "pharmaceutical compositions" comprising rifaximin. (*Id.*). Marchi disclosed that rifaximin can be used as an "antibacterial agent[]" in pharmaceutical compositions with conventional pharmaceutically acceptable excipients or carriers. (JTX 48 at 4:27-33, 4:67-5:4, 5:14-40, 60-62, 6:6-31, Cls. 10–11; Tr. 865:10-866:12, 868:20-869:3). The Normix Label disclosed that rifaximin was an approved antibacterial drug in Italy in 1985 as a coated tablet comprising 200 mg of rifaximin and pharmaceutically acceptable excipients. (JTX 94 at 5, 7-8; Tr. 867:13-17, 869:10-870:4, 903:3-9).

Norwich further argues that rifaximin's antibacterial properties were known. Cannata taught that rifaximin has outstanding antibiotic properties and has poor absorption, which indicates to a POSA that it could be used for GI treatments. (Tr. 862:22–24;

863:14–18). Marchi also disclosed "remarkable" antibacterial properties. (JTX 48 at 4:27-33, 4:67-5:4, 5:14-40, 5:60-62, 6:6-31, Cls. 10–11; Tr. 865:10-866:12, 868:20-869:3).

Salix did not respond to these arguments. (*See* D.I. 181 at 37–39).

The only difference between the previous pharmaceutical compositions of rifaximin and claim 36 is that claim 36 characterizes rifaximin as polymorphic form ß. Rifaximin ß is obvious over Cannata in view of common knowledge, for the same reasons as previously stated in connection with asserted claim 4 of the '199 patent. Accordingly, I find that a POSA would have had the motivation to combine the prior art references of Cannata, the Normix Label, or Marchi and Cannata, in view of the commonly known testing techniques, with a reasonable expectation of success in doing so. Salix offers no evidence or arguments to the contrary. Thus, Norwich has proved by clear and convincing evidence that claim 36 of the '206 patent is invalid as obvious.

3. Written Description

The asserted claims describe rifaximin ß as having XRPD peaks "at about 5.4°, 9.0°, and 20.9° 2θ." '199 Patent, Cl. 4, '206 Patent, Cl. 36. The specification states that rifaximin ß is "characterized . . . by a powder X-ray diffractogram (reported in FIG. 2) which shows peaks at the values of the diffraction angles 2θ of 5.4°; 6.4°; 7.0°; 7.8°; 9.0°; 10.4°; 13.1°; 14.4°; 17.1°; 17.90°; 18.30°; 20.9°." '199 Patent 5:64–6:3. Norwich argues that the polymorph patents improperly claim a genus, whereas the specification recites only a species. (D.I. 176 at 37–38).

Salix responds that (1) the claims, on their face, are limited to the specific polymorphic form rifaximin β, rendering Norwich's genus characterization inaccurate, and (2) even if Norwich is right, the claims identify structural features common to the genus as required by the caselaw. (D.I. 181 at 39–42). I agree with Salix on the first point, and accordingly will not address Salix's second argument.

The evidence shows that a subset of XRPD peaks can identify the polymorph. The "normal practice at the USPTO" is to claim a polymorphic form using "at least three powder diffraction pattern peaks." (Tr. 965:11–17; JTX 28 at XIFAX_NOR_0002208). Dr. Zaworotko's own patent explains, "For XRPD data herein, each composition of the present invention[, a new crystalline form of a known compound,] may be characterized by any one, any two, any three, any four, any five, any six, any seven, or any eight or more the 2θ angle peaks." (Tr. 916:17–917:18, PTX 707 at 15:36–39). I do not think the asserted claims claim a genus. They claim only rifaximin ß, a polymorphic form which can be identified using the three peaks recited in the claims.

Thus, I reject Norwich's written description challenge.

I. THE METHOD PATENTS

A. Inducement

1. Findings of Fact

1. At least some physicians will review Norwich's label.

2. Physicians will instruct patients to take rifaximin according to the instructions on the label.

2. Infringement

Before turning to a limitation-by-limitation infringement analysis for the method patents, I will address an underlying dispute regarding induced infringement when the patient is the one performing the patented method. Inducement requires direct infringement. Salix argues that either (1) the patients, in taking rifaximin, will directly infringe "because patients will read and follow the instructions in Norwich's Label (with or without the help of their physician)," or (2) physicians and patients will jointly infringe based on the label. (D.I. 174 at 4). I do not think there is joint infringement. I find that Plaintiffs have not shown that doctors condition the patient's receipt of a rifaximin prescription on the performance of particular steps in the way contemplated by *Akamai. See Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1023 (Fed. Cir. 2015) (en banc). Rather, the patients directly infringe.

According to Norwich, "Because patients will not take rifaximin correctly without physician instruction, the Norwich Label does not induce patients and cannot be the basis for finding specific intent." (D.I. 183 at 3–4 (citation omitted)). Essentially, because there is another party involved in the inducement (physicians), the "chain of events leading to infringement is . . . too attenuated to prove specific intent." (D.I. 183 at 6–7). I disagree. The Court of Appeals has long held, "the sale of a product specifically labeled for use in a patented method constitutes inducement to

infringe that patent[.]" *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011). In the context of a prescription medication, physicians have a particularly important role in conveying essential information to patients. The evidence in this case bears this out. (*See* Tr. 66:22-69:20; Tr. 119:5-120:16 (describing the process of prescribing rifaximin to patients)). Other areas of law, such as the learned intermediary doctrine, recognize the physician's essential role in communicating information about a medication to the patient. *See Reyes v. Wyeth Lab'ys*, 498 F. 2d 1264,1276 (5th Cir. 1974). A pharmaceutical company, such as Norwich, is well aware of how doctors prescribe medications to patients. Thus, if there will be direct infringement, then Norwich will have the specific intent to induce patients' direct infringement.

B. The HE Patents

HE is a liver disease that affects the brain. (Tr. 41:15-21; 48:10-16). For patients with HE, the liver does not properly filter toxins from the blood. These toxins can cause changes to the patient's mental state. (*Id.*) Physicians grade HE severity using the Conn score, which ranges from 0 to 4. (Tr. 45:14–47:4). Conn scores of 0 or 1 reflect a normal or near-normal mental state. A Conn score of 2 or higher reflects more serious symptoms, from obvious personality changes to stupor or even coma. (Tr. 46:6-11, 14-15). Conn scores of 0 and 1 cannot be detected in a routine physical exam. (Tr. 45:20–21; 46:4–5). Physicians also assess HE severity using an asterixis score. (Tr. 346:5–8). Asterixis occurs when a patient cycles between lower and higher levels of consciousness and can be measured by

tremors in a patient's outstretched hand. (Tr. 46:16–47:4).

HE can be either episodic or persistent. (Tr. 44:13–25). Persistent HE is characterized by a Conn score that remains at 2 or above. (Tr. 44:24–25). Patients with episodic HE have periods of remission punctuated by episodes of breakthrough overt HE. (Tr. 44:13–25; 45:14–46:15). An episode of "breakthrough overt HE" is an increase in the patient's Conn score to grade 2 or higher (e.g., going from 0 or 1 to 2 or more), or an increase in the patient's Conn and asterixis scores of one grade each with a baseline Conn Score of 0. (D.I. 149, Ex. 1 ¶ 81). Patients with a history of overt HE who are not currently having an overt HE episode are in "remission of HE." (*Id.* ¶ 81; Tr. 48:2–6). Thus, patients with a Conn score of 0 or 1 and no asterixis are in remission. (Tr. 48:2–6). After a first overt HE episode, only about half of patients will live one year. (Tr. 50:6–19).

Plaintiff asserts four method claims in connection with the HE patents.

Asserted Claim 6 of the '195 patent is a dependent claim with three elements: (1) reducing the risk of HE recurrence, (2) by orally administering about 550 mg of rifaximin twice daily (BID) to the adult subject, (3) for a period of 12 months or longer.

Asserted Claim 8 of the '573 patent is a dependent claim with three elements: (1) maintaining remission of HE, wherein remission is defined as a Conn score of 0 or 1, (2) by administering 550 mg of rifaximin to the subject BID, (3) for a period of 12 months or longer.

Asserted Claim 11 of the '397 patent is a dependent claim with four elements: (1) reducing a subject's risk of experiencing a breakthrough overt HE episode, (2) by orally administering to the subject 550 mg of rifaximin BID, (3) for a period of about 12 months or longer, (4) to a subject with a Conn score of 0 or 1.

Asserted Claim 12 of the '397 patent is a dependent claim with five elements: (1) reducing a subject's risk of experiencing a breakthrough overt HE episode, (2) by orally administering to the subject between about 1000 mg to about 1200 mg of rifaximin daily, (3) for a period of about 12 months or longer, (4) to a subject with a Conn score of 0 or 1, (5) "further comprising administering lactulose."

1. Findings of Fact

1. Norwich has knowledge of the HE patents.
2. Norwich's label will encourage administration of rifaximin for 12 months or longer.
3. Norwich's label will encourage administration of rifaximin for the "reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults."
4. Norwich's label will encourage administration in patients having a Conn score of 0 or 1.
5. Norwich's label will encourage at least some physicians to co-administer rifaximin and lactulose.
6. Patients will take rifaximin according to the instructions on the label and will directly infringe the asserted HE claims.

7. Norwich's label will induce infringement of the asserted HE claims.

8. The priority date of the asserted claims is October 2, 2008.

9. A POSA would have had a Ph.D. in pharmacology, biology, biomedical sciences, microbiology and/or an M.D. with board certification in gastroenterology. He or she would have had training in or experience with liver and GI disorder research. If needed, a POSA would have collaborated with others having ordinary skill in areas relevant to the claimed subject matter, including infectious diseases and microbiology.

10. The Salix Presentation was not publicly accessible as of the priority date and is not prior art.

11. Leevy 2007 does not disclose a method of administering rifaximin to maintain remission.

12. As of the priority date, a 12-month duration for the administration of rifaximin was not within the common knowledge of a POSA.

13. The claimed method met a long-felt need of reducing the risk of HE recurrence and maintaining remission.

14. There was skepticism in the industry regarding the long-term use of antibiotics to maintain remission in HE patients.

15. The HE patents are not invalid as obvious.

16. The specification describes using rifaximin with or without lactulose.

17. A POSA would recognize that the inventors had possession of the claimed method.

2. Infringement

i. Administering for 12 Months or Longer (All Claims)

It is more likely than not that Norwich's Label will encourage administration of the ANDA product for 12 months or longer in at least some patients, and that Norwich knows and specifically intends for this period of administration. Norwich's product is indicated for reducing overt HE recurrence. (JTX 73 § 1.2). HE is chronic. It must be managed until the patient gets a liver transplant or dies. I credit the testimony of Drs. Mahl and Brown that they have had HE patients maintain remission of HE for 12 months while on rifaximin 550 mg BID. (Tr. 120:21–24; Tr. 55:3–11). The label has no recommendation as to duration of administration. The label further describes a study in which some patients used the product for 12 months or longer. Taken together, this evidence demonstrates by a preponderance of the evidence that Norwich's label would encourage administering rifaximin for at least 12 months.

ii. Maintaining Remission ('573 Patent, Claim 8)

I find that Salix has proved by a preponderance of the evidence that Norwich's label instructs as to "maintaining remission of HE" as required by the asserted claims. Norwich's label is indicated for the "reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults." (JTX 73 § 1.2). The experts described "reducing the risk of overt HE recurrence" and

"maintaining remission of HE" as "basically synonymous" or a "continuum of the same thing." (Tr. 249:23–250:18, 252:9–18; Tr. 51:21–52:19). Remission is binary—either a patient is in remission or the patient is not. An overt HE recurrence ends remission. Thus, to maintain remission, a patient must avoid overt HE recurrence.

iii. Conn Score of 0 or 1 ('397 Patent, Claims 11 and 12)

Norwich's label will more likely than not induce use of rifaximin in patients with a Conn score of 0 or 1. The label encourages use to prevent an overt HE recurrence, which as I have found, means maintaining remission. The evidence shows that patients in remission of HE have a Conn score of 0 or 1. Thus, the label will encourage the use of rifaximin in patients who have a Conn score of 0 or 1. This conclusion is bolstered by the Clinical Studies section, which describes a clinical study in which the patients were "defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy." (JTX 73 § 14.2).

Norwich argues that (1) doctors do not calculate a Conn score for their patients before prescribing rifaximin, and (2) the Indications section does not reference the Clinical Studies section and thus it "merely describe[es] a parameter of the study, rather than actually encouraging, recommending, or promoting" the infringing use. (D.I. 183 at 10). I find these arguments unpersuasive.

The expert testimony shows that at least some physicians use Conn scores in clinical practice. (Tr. 154:2–22; 264:6–7). Defendant's expert, Dr. Mahl, testified that he does not calculate Conn scores but does

record the "elements that might go into a Conn score." (Tr. 114:16–20). The patents do not require the calculation of a Conn score. Rather, they require use in patients with a Conn score of 0 or 1, which can be present regardless of whether it has been calculated. On this testimony, it seems likely that Norwich's ANDA product will be used in at least some patients who have a calculated Conn score of 0 or 1 as well as patients whose Conn scores would be a 0 or 1, if calculated, based on the symptoms observed by their physicians.

Regarding the Clinical Studies section, the law does not require the indication section of a label to specifically direct the reader to look at other sections in order for those other sections to be considered. The Court of Appeals has held, "The jury was entitled to credit expert testimony regarding the label's instructions on who should take what drug, when, why, and how, and to reject the argument that certain portions of the label were disjointed from others." *GlaxoSmithKline LLC v. Teva Pharms. USA Inc.*, 7 F.4th 1320, 1329 (Fed. Cir. 2021), *petition for cert. filed*, No. 22-37 (July 11, 2022). I credit the testimony of Dr. Brown that physicians commonly read the Clinical Studies section. (Tr. 67:24–68:8). The "Hepatic Encephalopathy" subsection starts with the sentence: "The efficacy of rifaximin tablets 550 mg taken orally two times a day was evaluated in a randomized, placebo-controlled, double-blind, multi-center 6-month trial of adult subjects from the U.S., Canada, and Russia who were defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy (HE)." (JTX 73 § 14.2). Accordingly, I find that the label will induce use in patients with a Conn score of 0 or 1.

iv. Administration with Lactulose ('397 Patent, Claim 12)

Norwich's label will encourage co-administration with lactulose. In the Indications and the Clinical Studies section, the label notes that 91% of patients took rifaximin and lactulose concomitantly, and that lactulose did not alter the treatment effect of rifaximin. (JTX 73 §§ 1.2, 14.2). This strongly suggests that taking lactulose concomitantly is safe and effective, and it will likely encourage some physicians to administer rifaximin in conjunction with lactulose as required by the claims. I reject Norwich's comparison to *Shire LLC v. Amneal Pharmaceuticals*, which held that label indicating that a drug could be taken "with or without" food was "indifferent" as to which option was select and thus not an instruction to infringe. 2014 WL 2861430, at *5 (D.N.J. June 23, 2014), *aff'd in part, rev'd on other grounds*, 802 F.3d 1301 (Fed. Cir. 2015). The high percentage of patients who took lactulose concomitantly, and the fact that this information was included in the Indications section, encourages physicians to prescribe the two concomitantly.

I credit the testimony of Dr. Brown, who stated that the label, by citing the 91 percent figure, "makes clear that you can – you can and probably should use Lactulose in the majority of your subjects." (Tr. 76: 5–7). I further credit Dr. Brown's testimony, "Whenever possible, I use the combination of Lactulose and rifaximin because that's where the bulk of the data is." (Tr. at 76:12–13). I find that a physician reading the Norwich label and considering a study in which 91% of the patients were administered lactulose concomitantly

will be inclined to do so likewise "because that's where the bulk of the data" showing the efficacy of rifaximin is.

v. Substantial Noninfringing Use (All Claims)

Norwich argues that its ANDA product has substantial noninfringing uses, which is relevant to intent to induce. (D.I. 183 at 11–12). Most HE patients live less than 12 months after their first overt HE episode. Thus, a substantial number of patients taking Norwich's ANDA as directed will not take rifaximin for 12 months or more, and these uses will not meet the 12-month-or-more claim limitation. Norwich points to *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348,1363–66 (Fed. Cir. 2003) in support of this argument.

The Federal Circuit has distinguished *Warner-Lambert*, where the infringing use would be off-label use of the defendant's ANDA product and encompass only a small number of sales, and cases where "the proposed label itself recommends infringing acts." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117,1132–33 (Fed. Cir. 2018). Here, since I find that the label itself recommends infringement, the potential for substantial non-infringing uses does not negate Norwich's intent to induce infringement.

3. Invalidity

The parties agree that the definition of a POSA is not outcome determinative. (D.I. 176 at 2; D.I. 181 at 1). I adopt Plaintiffs' definition of a POSA.

Norwich argues that as of 2008, it was widely known that rifaximin was safe and effective for treating HE. (D.I. 176 at 3). Rifaximin was indicated abroad for HE in 2000. (JTX 94 at 5, 9). In 2004, the FDA approved Salix's Xifaxan for traveler's diarrhea. From that time, there is evidence of widespread off-label use of Xifaxan by physicians to treat patients with HE. Market research conducted by Salix shows that, by January 2007, 77% of physicians who treated HE patients had prescribed Xifaxan for HE. (DTX 349-16).

The prior art described the use of rifaximin in HE patients. For instance, a 1993 article ("Festi") described one open study and two randomized, controlled, comparative studies. The three studies "confirm[ed] the usefulness of rifaximin in the management of cirrhotic patients with mild HE." (JTX 42 at 607; Tr. 165:11-166:5). A 2000 article ("Williams 2000") described a study confirming that 1200 and 2400 mg doses of rifaximin showed significant improvement "in reducing objective parameters of HE in cirrhotic patients," and "treatment with rifaximin 1200 mg/day may be considered as an adjuvant or an alternative" to lactulose, with no adverse effects. (JTX 66 at 203-4, 207). Lactulose was the "mainstay" for HE therapy at the time. (*See* Tr. 203:17–204:5). In 2004, doctors at a Salix-hosted conference on hepatology reported being "very happy with [rifaximin's] results" and that rifaximin had "excellent" tolerability with "no significant side effects." (Tr. 172:10–18; 174:8-22; DTX 584-1, 3). A 2007 retrospective chart review ("Leevy 2007") showed better treatment outcomes for patients on rifaximin than on lactulose. (DTX 390-3; Tr. 204:6-16).

Norwich also points to retrospective chart reviews published after the priority date that show use of rifaximin for HE before the priority date. (*See* D.I. 176 at 9–10 (citing JTX 111, JTX 109)). I do not think these uses are in the prior art because there is no evidence that a POSA would have known about them. They do provide evidence of a POSA's state of mind, since the physicians prescribing Xifaxan off-label meet both parties' definition of a POSA. (*See* D.I. 182 ¶ 121; D.I. 177 ¶ 1). *See In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1025 (Fed. Cir. 2018) (holding, "The district court . . . properly relied on [a reference] not as statutory prior art, but for the fact that [POSAs] were interested in pursuing less frequent dosing regimens.").

i. Prior Art Combinations

Norwich presents two obviousness combinations for the asserted HE claims: the Bausch HE Study in light of the Salix Presentation, and Leevy 2007 in light of common knowledge. I will consider each in turn.

The Bausch HE Study is the protocol for the clinical trial that ultimately led to the approval of rifaximin for HE. It disclosed the method, dosage, lactulose, and Conn score limitations of the asserted claims. The Salix Presentation was a presentation given by Dr. Leevy at a Salix shareholder's meeting in which Dr. Leevy described using rifaximin to treat HE. (DTX 52-4). Dr. Leevy described the duration limitation. Between the two, all claim limitations are disclosed.

Salix argues that the Salix Presentation was not in the prior art because it was not accessible. (D.I. 181 at 4). Salix tried to exclude the evidence before trial.

(D.I. 150). I denied Salix's motion without prejudice to evaluating its prior art status based on a complete understanding of the record. (D.I. 161 at 28:9–18). Norwich's response to the motion in limine relied on evidence that Norwich did not present at trial. (*See* D.I. 150 at 9 of 18 (describing a Salix press release announcing the conference)). Accordingly, I will reconsider the question in light of the evidence presented at trial.

At trial, Defendant offered the transcript of the Salix Presentation and expert testimony regarding the presentation. (DTX 660; Tr. 175:20–176:22). Defendant's expert, Dr. Berg, testified that the Salix presentation was publicly available online at the SEC and that a POSA would be motivated to find it because Salix was the only company selling rifaximin in the United States at the time. (Tr. 175:22–24; 176:15–22). Salix responds that this testimony is unsupported by explanation or evidence. (D.I. 181 at 4–5). While I credit Dr. Berg's assertions regarding a POSA's motivation to look for and methods of finding such a document, I do not credit his testimony regarding the availability of the Salix Presentation online before the priority date. I do not think a medical doctor's expertise is a basis for opining on what the SEC had available online more than a decade ago. Dr. Berg's opinion is not supported by independent evidence. "At this critical point in the determination of obviousness, there must be factual support for an expert's conclusory opinion." *Upjohn Co. v. Mova Pharm. Corp.*, 225 F.3d 1306, 1311 (Fed. Cir. 2000). Without evidence of online accessibility, and without evidence that the meeting was attended by interested POSAs (or even directed to POSAs, rather than investors), I find that

Defendant has not shown by clear and convincing evidence that the Salix Presentation is prior art.

Norwich's second prior art combination is Leevy 2007 and common knowledge. Norwich argues, "Leevy 2007 disclosed the method, dosage, and Conn score limitations." (D.I. 176 at 8). Norwich argues that common knowledge supplies the missing limitations of duration (of 12 months or more) and lactulose. (*Id.* at 9).

Upon review of the evidence, I find that Leevy 2007 does not describe the method limitation. Independently, common knowledge cannot supply the duration limitation. I will address each in turn.

The claims are directed to maintaining remission or reducing the risk of breakthrough overt HE. Leevy 2007 concluded that HE hospitalizations were less frequent and shorter for patients on rifaximin than for patients on lactulose. Norwich argues that these hospitalizations are a metric for breakthrough overt HE and therefore Leevy 2007 discloses the method limitation. (D.I. 176 at 8). But Norwich's argument is not supported by the record. Norwich's expert, Dr. Berg, testified as to Leevy 2007's disclosure of rifaximin's ability "to treat HE" or as "therapy for HE." (*E.g.*, Tr. 181:9–18; 206:2–10). He did not characterize it as disclosing prevention or the like. I see no testimony linking Leevy's reduction in hospitalizations with the claimed method of preventing breakthrough overt HE.

Furthermore, Leevy 2007 did not track Conn scores throughout the study. As Salix argues, "a POSA would not have been able to determine whether subjects who had a Conn score of 1 at the beginning of the rifaximin phase maintained that Conn score throughout the 6 months." (D.I. 181 at 5). I credit Dr. Brown's

testimony, "You cannot interpret the natural course of these patients' HE through the six-month period based on the data provided." (Tr. 393:4–6). Leevy 2007 does not teach the maintaining remission limitation.

Thus, Leevy 2007 cannot supply the limitations required for the asserted claims, whether it is maintaining remission of HE or reducing the risk for breakthrough overt HE. On that basis alone, Defendant fails to prove obviousness.

There is a second, independent basis to reject the prior art combination of Leevy 2007 and common knowledge. I do not think that a POSA would have a reasoned basis to resort to the "common sense" that rifaximin could be used for 12 months or longer. Common sense can supply a limitation missing from the prior art if a "searching" review of the prior art provides a "reasoned basis for resort to common sense." *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1363 (Fed. Cir. 2016).

Many of the sources Norwich relies upon to show long-term administration are not prior art. (*See* D.I. 176 at 9–10 (citing retrospectives published after the priority date and the Salix Presentation)). They were not, at that point, in the common knowledge of the field.

Administration of rifaximin for 12 months or more suggests prevention (i.e., maintaining remission or reducing the risk of overt HE recurrence), not mere treatment. Norwich argues, "[T]he record is replete with prior art disclosing the use of rifaximin in patients in remission from HE (i.e., having a Conn score of 0 or 1)." (D.I. 185 at 5–6). It is true that some of the studies included patients with Conn scores of 0 or 1.

(JTX 66 at 205; JTX 42 at 607.) Many of these patients would have been in remission, but the sources discuss HE "treatment," not prevention or maintenance of remission. The Bausch HE study was the first prior art source to clearly articulate a desire to prevent hepatic encephalopathy. (DTX 52-4). As of the priority date, the Bausch Study did not have any results. Accordingly, I do not think that a 12-month treatment period was within the common knowledge as of the priority date.

Furthermore, Salix has presented evidence that a POSA would have known that long-term administration of rifaximin, an antibiotic, was risky. Not only could long-term use of antibiotics lead to a superinfection, which could kill the patient, but, "A POSA would have been concerned that if an HE patient developed clinical resistance to rifaximin, [the POSA] would not be able to administer rifaximin the next time the patient experienced an HE episode." (D.I. 181 at 11; Tr. 388:3–9). The parties' experts disagreed about the level of risk associated with long-term administration of rifaximin and how a POSA would consider that risk. I credit Dr. DuPont's testimony that without further studies, a POSA would have been reluctant to administer rifaximin long-term. (Tr. 467:7–12). Thus, I think that the prior art does not provide enough of a reasoned basis for supplying the duration limitation.

Finally, Salix has presented evidence of secondary considerations of nonobviousness that weigh in favor of finding the HE patents nonobvious. The claimed HE methods met a long-felt need for maintaining remission and reducing the risk of breakthrough overt HE episodes. Salix argues, "As of October 2008, no

drug had been approved for HE in over 30 years, and no drug had ever been approved to *prevent* HE recurrence." (D.I. 174 at 17). Norwich's expert responded that there was no need because physicians were already using a combination of rifaximin and lactulose to treat HE. (Tr. 222:7–20). As Salix points out, however, "Short-term, off-label use of rifaximin to *treat* HE did not meet a long-felt need for long-term *prevention* of HE recurrence." (D.I. 186 at 10).

There was also some skepticism in the industry. Salix points to comments from the FDA advisory committee expressing the concern "that indefinite use of rifaximin could change the gut flora and cause antibiotic resistance." (D.I. 174 at 17). Norwich argues that the FDA statements lack a nexus to the asserted claims. I disagree. "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1330 (Fed. Cir. 2017) (citation omitted). But here, the potential antibiotic resistance would have resulted from the claimed method of treatment. Accordingly, I give some weight to the FDA comments as evidence of skepticism.

Ultimately, I find that Norwich has not shown by clear and convincing evidence that the asserted HE claims are invalid as obvious.

ii. Written Description

Norwich argues, "Claim 8 of the '573 patent, claim 6 of the '195 patent, and claim 11 of the '397 patent are invalid for lack of written description because the specifications of the patents fail to show that the

administration of rifaximin alone (*i.e.*, in the absence of concomitant administration of lactulose) achieves the claimed effects." (D.I. 181 at 16). Norwich's argument seems to be that the specifications lack data supporting the efficacy of rifaximin alone. (*See id.*). This is not the standard for written description. The specifications all describe using rifaximin with or without lactulose. (JTX 19 at 16:62-17:3 ("This method includes: administering rifaximin to a subject daily that is being treated with lactulose, and tapering lactulose consumption . . . . In one embodiment, the baseline use of lactulose is no use."); JTX 11 at 16:62-17:3; JTX 22 at 10:49-57). I therefore find that Norwich has not shown a lack of adequate written description by clear and convincing evidence.

C. THE IBS-D PATENTS

Irritable bowel syndrome ("IBS") is characterized by symptoms including abdominal pain, bloating, frequency, urgency, gas, and changed bowel habits, such as diarrhea, constipation, or alternating diarrhea and constipation. (E.g., Tr. 618:23–620:2). Subtypes of IBS include IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), or IBS with alternating diarrhea and constipation (IBS-A). (Tr. 622:9–623:1). The IBS-D subtype comprises about one-third of IBS patients. (Tr. 622:21–623:1). IBS may be caused, for example, by abnormal motility, abnormal muscular coordination, changes in the microbiome in the colon or small intestine, intolerance to certain foods, or psychological factors. (Tr. 618:23–620:2).

Plaintiffs assert two claims in connection with the IBS-D patents.

Asserted Claim 3 of the '667 patent is a dependent claim that has three elements: (1) administering 550 mg of rifaximin three times a day (TID) for 14 days; (2) to treat one or more symptoms of IBS-D; (3) in a subject 65 years of age or older.

Asserted Claim 2 of the '569 patent is a dependent claim with two elements: (1) administering 550 mg of rifaximin TID for 14 days; and (2) after stopping rifaximin, achieving a durability of response that comprises about 12 weeks of adequate relief of symptoms.

1. Findings of Fact

1. Norwich is aware of the IBS-D patents.
2. Norwich's label will encourage administering rifaximin to adults aged 65 years or older with IBS-D.
3. Norwich's label will encourage administration of "one 550 mg tablet taken orally three times a day for 14 days" for the treatment of IBS-D, which inevitably will result in at least some patients having a durability of response comprising about 12 weeks of adequate relief after stopping rifaximin.
4. Patients will take rifaximin according to the label and will directly infringe the asserted IBS-D claims.
5. Norwich's label will induce infringement of the asserted IBS-D claims.
6. The priority date for the IBS-D claims is February 26, 2008.

7. A person of skill in the art would have had a medical degree with training in gastroenterology or have been a practicing physician, such as an internist, with experience in treating IBS.

8. The prior art includes the '608 patent (JTX 132), the Pimentel Book (PTX 752), Yang (DTX 892), the RFIB 2001 Press Release (DTX 657), Pimentel 2006 (JTX 53), the RFIB 2001 Protocol (DTX 340), Cuoco (JTX 38), Barrett (JTX 71), Viscomi 2005 (JTX 64), Lin 2006 (JTX 69), Lauritano (DTX 384), and Scarpellini (JTX 60).

9. The RFIB 2001 Protocol and Pimentel 2006 disclose all limitations of the IBS-D claims.

10. A POSA would have been motivated to combine the RFIB 2001 Protocol and Pimentel 2006 with a reasonable expectation of success.

11. As of the priority date, the prior art disclosed positive results in using rifaximin to treat IBS-D for a range of doses. The asserted IBS-D claims describe a dosing regimen within the known range.

12. A POSA would have had motivation to treat IBS-D patients 65 years of age or older with rifaximin. A POSA would have had a reasonable expectation of success in treating this patient group with rifaximin.

13. The prior art did not teach away from using rifaximin to treat IBS-D according to the claimed methods.

14. There was some skepticism in the literature.
15. The asserted IBS-D claims are invalid as obvious.
16. The specification describes "durability of response" as including adequate relief from symptoms for 12 weeks.
17. A POSA would recognize that the inventor possessed the claimed durability of response.
18. A POSA would have reasonable certainty regarding the meaning of "adequate relief" and "durability of response."

2. Infringement

i. Age 65 and Over ('667 Patent, Claim 3)

Claim 3 of the '667 patent requires administration of rifaximin to patients who are 65 years and older. I find that Norwich's label will induce administration to this patient population. Norwich's ANDA product is indicated for "adults." (JTX 73 § 1.3). "Adults" include people who are 65 years and older. The label's "Use in Special Populations" section describes "Geriatric Use." (JTX 73 § 8.5). The label states, "No overall differences in safety or effectiveness were observed between these subjects [aged 65 and over] and younger subjects for either indication." (*Id.*)

Accordingly, Norwich knows and specifically intends that its ANDA product will be used to treat IBS-D in patients who are 65 and older.

ii. 12 Week Durability of Response ('569 Patent, Claim 2)

Claim 2 of the '569 patent requires a "durability of response [that] comprises about 12 weeks of adequate relief." I find that Norwich's label will induce such a response in at least some patients. Salix argues, "By following [the dosing] instructions [on the label], some patients will inevitably have a durability of response comprising about 12 weeks of adequate relief" (D.I. 174 at 14). Salix's expert testified to this, and Norwich's expert admitted as much. (Tr. 537:12–540:4, 581:16–22 (agreeing that at least some patients "will experience adequate relief of their IBS-D symptoms for 12 weeks after taking rifaximin 550 milligrams three times a day for 14 days")). "[A]n accused product that sometimes, but not always, embodies a claimed method nonetheless infringes." *Bell Commc'ns Rsch., Inc. v. Vitalink Commc'ns Corp.*, 55 F.3d 615, 622–23 (Fed. Cir. 1995).

Norwich's label supports a finding of inducement. The product is indicated "for the treatment of irritable bowel syndrome with diarrhea." (JTX 73 § 1.3). The Clinical Studies section states, "The efficacy of rifaximin tablets for the treatment of IBS-D was established in 3 randomized, multi-center, double-blind, placebo-controlled trials in adult patients." (JTX 73 § 14.3). The third study, TARGET 3, tracked long-term response to treatment. In it, "382 [patients] experienced a period of symptom inactivity or decrease that did not require repeat treatment by the time they discontinued, including patients who completed the 22 weeks after initial treatment with rifaximin." (*Id.*). Norwich argues that TARGET 3 only measured two

symptoms of IBS-D, rather than the claimed "adequate relief" of IBS-D symptoms, and that it reported "time to recurrence" rather than the claimed "durability of response." (D.I. 183 at 14). Even when a proposed label does not exactly track the claim language, a package insert containing directives that will "inevitably lead some consumers to practice the claimed method" provides sufficient evidence for a finding of specific intent. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). Accordingly, I find that Norwich's label will induce some patients to experience a 12-week durability of response as required by the patents and that Norwich will have the specific intent to induce infringement.

3. Obviousness

Salix asserts that the definition of a POSA is not outcome determinative. (D.I. 181 at 16). Noriwch has proposed that a POSA would have had a medical degree with training in gastroenterology or have been a practicing physician, such as an internist, with experience in treating IBS. (D.I. 181 at 17). I adopt Norwich's definition of a POSA.

Norwich argues that, as of the priority date, rifaximin was known to be safe and effective in treating IBS-D. Prior to February 2008, there was widespread off-label use of Xifaxan to treat IBS in the United States. As of January 2008, 74% of gastroenterologists polled by Salix had prescribed Xifaxan for IBS. (DTX 349-130). Prescription data showed that 27.7% of Xifaxan 200 mg tablet uses in November 2007 had been for IBS. (DTX 349-89; Tr. 832:2-833:23).

The prior art also discussed using rifaximin to treat IBS. In 1999, Dr. Pimentel applied for patents

on the use of rifaximin to treat IBS. (JTX 132; JTX 133; Tr. 617:1-21). The '608 patent claims a method of "treating a subject suffering from [IBS], comprising administering rifaximin to the subject . . ." (JTX 132 at cl. 1; Tr. 620:3-621:9).[2] At a 2005 conference hosted by Salix, Dr. Pimentel disclosed that his practice group had used rifaximin to treat about 900 patients. (Tr. 627:7-628:5; DTX 582-4, 5). In 2006, Dr. Pimentel published a book titled *A New IBS Solution, Bacteria – the Missing Link in Treating Irritable Bowel Syndrome*, which recommended the use of rifaximin as a safe and effective way to treat IBS-D. (PTX 752; Tr. 623:25-624:21).

In 2006, three studies were published on the use of rifaximin to treat IBS. A randomized, double-blind, placebo-controlled study found rifaximin to be more effective than placebo in improving IBS. ("Pimentel 2006," JTX 53). A retrospective chart review of IBS patients who had tested positive for small intestine bacterial overgrowth ("SIBO") reported a significant reduction in the number of patients having IBS symptoms 4-5 months after treatment, and that 12 of 23 patients had "complete resolution of IBS symptoms." ("Cuoco," JTX 38 at 94). Another retrospective chart review of 8 patients disclosed, "rifaximin use resulted in complete resolution of clinical symptoms in 4 patients, with no IBS relapse (follow-up, 1 to 6 months)," and "partial symptom improvement was observed in 4 patients, 3 of whom were treated for an additional 2 months with rifaximin 400 mg three times daily cycle

[2] The '608 patent issued in 2010 but the parties agree that it was publicly accessible before the priority date. (D.I. 149, Ex. 1 ¶ 136).

therapy (2 weeks on / 1 week off []) which resulted in a 50% to 70% improvement from baseline." ("Barrett," JTX 71; Tr. 639:9-640:5).

Norwich proposes three prior art combinations involving three pieces of prior art. Because I agree that Pimentel 2006 in light of the RFIB 2001 Protocol renders the asserted claims of the IBS-D patents obvious, I will not address the other two combinations.

Pimentel 2006 administered rifaximin, 400 mg TID for 10 days, to treat IBS patients aged 18-65. Pimentel 2006 taught, "rifaximin resulted in statistically greater global improvement in IBS than placebo," and "[i]mprovements were sustained through 10 weeks of follow-up" after 10 days of treatment. (JTX 53 at 562).

The "RFIB 2001 Protocol" (DTX 340) was a Phase II trial designed to administer rifaximin to patients aged 18 and over, 550-2,220 mg per day for 14 days for the treatment of IBS-D. The protocol included the outcome measures of providing adequate relief of symptoms and evaluating a durability of response over a 12-week post–treatment period. Salix announced the successful completion of this study on September 5, 2007 (the "RFIB 2001 Press Release") and disclosed, "Top-line results of this study demonstrate that . . . a 14-day course of rifaximin at 550 mg twice-a-day, provides a statistically significant improvement in both adequate relief of IBS symptoms and adequate relief of bloating, compared to placebo." (DTX 657-4; Tr. 656:12-657:10).

The RFIB 2001 Protocol and Pimentel 2006 disclose all limitations of the asserted IBS-D claims.

I find that a POSA would have been motivated to combine Pimentel 2006 with the RFIB 2001 Protocol and would have had a reasonable expectation of success. Pimentel 2006 reported sustained improvement in IBS symptoms for patients aged 18-65 for at least 10 weeks on a 400 mg TID, 10-day regimen. The RFIB 2001 Protocol included no upper age limit, a 14-day dosing regimen of 550 to 2200 mg per day, and the treatment of patients with IBS-D in particular. As of the priority date, a POSA would have known about the successful RFIB 2001 Protocol results. Widespread off-label use reflects a motivation to use rifaximin for the treatment of IBS-D with a reasonable expectation of success. As described above, several pieces of prior art reported success in treating IBS with rifaximin. The caselaw does not require "conclusive proof of efficacy." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014). Rifaximin had been shown to be effective in treating IBS in Pimentel 2006 and IBS-D in the RFIB 2001 Protocol, which were randomized, placebo-controlled clinical trials. Together, I think this is strong evidence that a POSA would have a motivation to use rifaximin for the treatment of IBS-D.[3]

---

[3] The parties do not discuss whether there is any difference between the motivation to use rifaximin to treat IBS and to treat IBS-D. I think a POSA would have been motivated to treat IBS-D and would have had a reasonable expectation of success in doing so, even though much of the prior art describes the treatment of "IBS." About one third of IBS patients have IBS-D, and there is no evidence in the record that a POSA would expect an IBS-D patient to respond differently to treatment than a patient with another form of IBS. (Tr. 622:21-623:1).

I also find that a POSA would have had the motivation to select an optimal dosing regimen from within the known range. The prior art describes positive results from a range of doses. Pimentel 2006 used 400 mg of rifaximin TID for 10 days and reported "global improvement in IBS." (JTX 53 at 558). Cuoco disclosed a total dose of 1200 mg for 14 days and reported significant reduction in the number of patients having IBS symptoms. (JTX 38 at 91). Barrett disclosed 400 mg TID for 1-5 months. (JTX 71). In 2007, Quigley explained, "Antibiotic dose and duration of therapy have not been established. All studies to date have used different doses and antibiotic regimens; the optimal approach needs to be established in a prospective, placebo-controlled, dose-ranging study." (PTX 692 at 1142). The RFIB 2001 Protocol taught a range from 1100 mg to 2200 mg per day for 10-14 days. (Tr. 655:20-656:11). The RFIB 2001 Press Release reported that a "14-day course of rifaximin at 550 mg twice-a-day" dosage saw effective results. (DTX 657-4). The claimed dose is 550 mg of rifaximin TID for 14 days.

"Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or working ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (cleaned up). Here, a POSA would have been motivated to combine the prior art to achieve a dosage regimen within the known range. Salix's market research showed that 56% of physicians who prescribed Xifaxan for IBS used TID dosing and 62% had prescribed the drug to be taken for 10-14 days. (DTX 349-131). This market research is not prior art because it was not publicly available as of the

priority date, but it reflects a POSA's state of mind. Pimentel 2006 taught, "Recent data suggest that the optimal dosage of rifaximin may, in fact, be higher than that used in our study." (JTX 53 at 562). A POSA would have been motivated to use TID dosing to maintain an effective concentration of rifaximin in the small intestine to control bacteria levels. (Tr. 672:4-23). Finally, a POSA would have been motivated to improve the use of rifaximin to treat IBS by using a larger tablet to reduce patients' pill burden and improve compliance. (Tr. 674:1-16.).[4]

I further find that a POSA would have had the motivation to treat patients 65 years of age or older with a reasonable expectation of success. The prior art described rifaximin use to treat symptoms of IBS-D patients 65 years or older. (JTX 71 at 1-2; DTX 340-7; DTX 657-4). A POSA would have expected the effect observed in Pimentel 2006 to apply to older patients too. (Tr. 679:12-16).

Salix attacks Norwich's obviousness case on several fronts.

---

[4] Salix argues that Dr. Harary undermined his own testimony on the pill burden. Dr. Harary testified, "I don't think going from two pills to one pill would make a big difference, but if you have a larger number of pills, then going to one pill would be – would be convenient and the patients would be more comfortable taking them." (Tr. 674:12–16). As of the priority date, only 200 mg pills were available. I take Dr. Harary's testimony to be saying that three 200 mg pills would be needed to achieve a similar dose (600 mg, as opposed to the claimed 550 mg), and that three pills are more inconvenient than one pill. Accordingly, I do not see how Dr. Harary undermined his own testimony regarding pill burden.

Salix argues that a POSA would recognize these prior art sources as flawed. Cuoco, for instance, is based on the unproven premise that SIBO contributed to IBS-D. Furthermore, its methodology was poor. (D.I. 181 at 19). Barrett was a retrospective chart review of only 8 patients and concluded that more research was needed. (*Id.*). Pimentel 2006 did not find an improvement in the symptoms of abdominal pain and diarrhea. (JTX 53 at 561). An editorial by Dr. Drossman noted that Pimentel 2006's limitations made its "findings inconclusive and raise[d] questions about the clinical significance of the results." (PTX 457 at 627; Tr. 767:11-18, 770:10-19). Finally, Salix argues that the RFIB 2001 Protocol did not disclose results, and "it was unrebutted that a POSA would not have reasonably expected RFIB2001 would be successful simply because the trial had begun." (D.I. 181 at 19–20).

I am unpersuaded by these arguments. It is fair to critique sources, and a POSA would take a source's shortcomings into consideration when evaluating the evidence. Obviousness does not require perfect evidence, however, and the available evidence persuaded a significant number of doctors who would have been qualified as POSAs to use rifaximin to treat IBS. Regarding Pimentel 2006's failure to find an improvement in abdominal pain and diarrhea, the patents are not directed to specific symptoms but to "adequate relief." There are many symptoms of IBS-D. The patents themselves do not claim relief from every symptom.

Finally, I find that Salix's press release disclosing success in the RFIB 2001 Protocol study is prior art, and thus a POSA would have known about the RFIB

2001 top-line results as of the priority date. Salix argues that the press release was derived from the inventor's work and thus cannot be prior art. (D.I. 181 at 20 (citing *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1380-81 (Fed. Cir. 2005))). Norwich argues that Salix has waived this contention by failing to raise it in the Pretrial Order. (D.I. 185 at 8). Upon review of the Pretrial Order and its Exhibits (D.I. 147-149), I see Plaintiffs' acknowledgement that Norwich is asserting the press release as prior art (D.I. 149, Ex. 4, at 5 n.2), and I see a list of items the prior art status of which Plaintiffs contest, which does not include the press release (*id.* at 6 ¶28), and I do not see any discussion of derivation, so the argument is likely waived. But I do not need to decide waiver, however, because there is no evidence upon which to make a factual finding that the press release was derived from the inventor's work. "Since appellees have produced no evidence—unsurprising given their belated recourse to this argument—and provided no supported explanation demonstrating that the Brandt references were in fact printed publications authored by Dr. VanDenburgh for the purposes of § 102(a), we see no reason to remand to make further findings on this issue." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 969 (Fed. Cir. 2014). The *Allergan* Court thus concluded that the printed publications at issue were prior art. *Id.* at 969–70). The press release is therefore prior art. Its disclosure of positive results would give a POSA a reasonable expectation of success in using rifaximin to treat IBS-D.

Salix also points to skepticism in the literature regarding the connection between SIBO and IBS and whether to use antibiotics to treat IBS-D. Drossman

criticized the Pimentel 2006 methodology, as discussed above. A 2007 Education Practice note by Eamonn M.M. Quigley stated, "sound rationale for antibiotic therapy ha[d] not been established because the issue of SIBO in IBS ha[d] not been resolved." (PTX 692 at 1142; Tr. 777:20–21). Indeed, Salix argues, using antibiotics would have drawbacks: antibiotics could "exacerbate symptoms" or "lead to antibiotic resistance and opportunistic infections" like *c. difficile*. (PTX 664 at 1780; PTX 692 at 1142). A February 4, 2008 article by Vanner considered the evidence and concluded that there was insufficient evidence to recommend the use of antibiotics to treat IBS. (Tr. 779:3–8). Accordingly, Salix argues that the off-label use is best understood as physicians acting out of "desperation, not because they expected it to work." (D.I. 181 at 17).

Upon review of the evidence, it appears that IBS is a complex disease and the pathogenesis was unknown as of the priority date. The relationship between IBS and SIBO was actively being explored, provoking a debate within the field. Quigley, Vanner, and Drossman do not teach away from using rifaximin to treat IBS, and Salix does not argue that they do. Based on the evidence, I do not think a POSA would elevate these sources above the other prior art available. The RFIB 2001 Press Release—which was not cited by Quigley, Vanner, or Drossman—states, "The belief that bacteria in the small bowel may play a role in the symptoms of IBS gains additional evidence with this large, multicenter trial." (DTX 657-4). I do not think a POSA would have discounted prior art sources that were based upon the theory that SIBO contributed to IBS because studies such as the RFIB 2001

Protocol were testing that hypothesis at the time. More importantly, a POSA would look to the top-line results from the RFIB 2001 Protocol as evidence that rifaximin could be effective in treating IBS-D, regardless of whether the results were based upon a link between IBS-D and SIBO.

Regarding the concerns of bacterial resistance, expert testimony shows that short-term administration did not raise resistance concerns. (Tr. 493:15-494:20). Furthermore, in 2007, a retrospective study of 84 IBS patients who were retreated with rifaximin noted that 69% of patients had a "clinical response" to rifaximin and that retreatment did not result in clinically relevant antibiotic resistance. (DTX 892-2, 5; Tr. 630:5-19, 631:9-18).

Accordingly, I do not think these concerns would dissuade a POSA from exploring the use of rifaximin in treating IBS-D. The 74% of gastroenterologists who had reported using rifaximin for IBS-D patients is real world evidence supporting the conclusion that there was a motivation to explore this treatment, despite the potential risks.

Regarding secondary considerations, Salix argues that there was skepticism that the claimed dosing regimen could safely and effectively treat IBS-D. (D.I. 174 at 17). Salix points to statements in Quigley, Drossman, and Vanner such as, "A sound rationale for antibiotic therapy has not been established . . . . ," and, "There is insufficient evidence to recommend antibiotics for the treatment of [IBS] at present." (PTX 692 at 1142; PTX 693 at 1319). Furthermore, experts on the FDA advisory committee stated that using rifaximin

550 TID for 14 days was "a completely different paradigm and a different treatment structure," and that Salix had proposed to "treat[] a disease which we know nothing or very little about with a drug that we know little or nothing about." (PTX 535 at 302, 307). The FDA advisory committee also expressed concern about antibiotic resistance. (*Id.* at 137).

Norwich responds that Salix's evidence of skepticism "fails" because rifaximin had already been used to safely and effectively treat IBS-D before 2008. (D.I. 183 at 18). I do not think this negates Salix's evidence of skepticism.

Regarding skepticism in the literature, Norwich argues that one of the articles was published before Yang and the RFIB 2001 Press Release, and the other two articles did not cite those references. (*Id.* at 20). I agree that evidence of skepticism is not as powerful when the skepticism is expressed by a source unfamiliar with the "prior art references that laid the groundwork for the inventors' experiments." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1365 (Fed. Cir. 2007). I still give some weight to these articles, especially Vanner, which was published less than a month before the priority date.

Regarding the FDA advisory committee, Norwich argues, "The cited passages from the 2011 FDA advisory committee meeting regarding the IBS-D indication did not criticize the safety or effectiveness of rifaximin to treat IBS-D in at least some patients." (*Id.* at 19). Norwich's expert did not address the FDA statements. I decline to adopt attorney argument in place of expert testimony.

Ultimately, I give some weight to Salix's evidence of skepticism from the literature and the FDA's statements. I do not think these experts "expressed disbelief," *United States v. Adams*, 383 U.S. 39, 52 (1966), but there is a "range of third-party opinion that can constitute skepticism." *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1378 (Fed. Cir. 2019). Ultimately, Salix has shown a small amount of skepticism but not enough to change the outcome of the obviousness analysis.

I find that the asserted IBS-D claims are invalid as obvious.

4. Written Description

Norwich argues that asserted claim 2 of the '569 patent lacks written description because it fails to show possession of the claimed "durability of response compris[ing] about 12 weeks of adequate relief of symptoms." (D.I. 176 at 30). The specification explains:

> As used herein, 'durability of response' includes for example, adequate relief of symptoms after removal of treatment, continuous adequate relief of symptoms after removal of treatment, or response that is greater than or superior to placebo response. . . . The duration of response, may be, for example, 2 days, 7 days, two weeks, 3 weeks, 4 weeks, 12 weeks, between about 1 week and about 24 weeks or longer.

'569 Patent at 11:44–53. The specification also discloses a proposed study design in Figure 3 "to show durability of response." *Id.* at 6:10–12. Figure 3 shows a "4 Week Treatment Period" follow by a 12 week

"Post-Treatment Phase." *Id.* at Fig. 3, 25:55–59. I think this is enough to show possession of the claimed 12-week durability of response.

Norwich argues that the disclosure is "effectively unlimited in time." (D.I. 176 at 31). "[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Here, the evidence shows that IBS-D is a complex disease and that not all patients achieve a 12-week durability of response. A POSA would recognize that the inventor adequately described a range of possibilities for the durability of response and was in possession of the claimed 12-week period.

5. Indefiniteness

Norwich argues that asserted claim 2 of the '569 patent is invalid as indefinite. (D.I. 176 at 28). As noted, Claim 2 includes the limitation, "durability of response compris[ing] about 12 weeks of adequate relief of symptoms." Norwich argues that "adequate relief of symptoms" is subjective opinion. (*Id.*). Salix responds that "adequate relief" and "durability of response" have accepted meanings to a POSA. (D.I. 181 at 31). IBS-D is a collection of symptoms and there is no biomarker to determine a successful overall treatment of IBS-D. (Tr. 507:24-508:7). I credit Dr. Schoenfeld's testimony that patient-reported "adequate relief" is used to determine IBS-D treatment success in the field. (Tr. 519:15-22; 821:9-822:1). Thus, I reject Norwich's argument that claim 2 of the '569 patent is invalid as indefinite.

V. CONCLUSION

For the foregoing reasons, Norwich's ANDA will induce infringement of the HE, IBS-D, and Polymorph patent claims. The HE claims are nonobvious and Norwich has failed to show a lack of adequate written description. The asserted Polymorph and IBS-D claims are invalid as obvious.

I will enter a final judgment in accord with the conclusions of this opinion.

APPENDIX C

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE

SALIX PHARMACEUTICALS, LTD.; SALIX PHARMACEUTICALS, INC.; BAUSCH HEALTH IRELAND LTD.; ALFASIGMA S.P.A.,
Plaintiffs,
v.
NORWICH PHARMACEUTICALS, INC.,
Defendant.

Civil Action No. 20-430-RGA

Filed: May 17, 2023

MEMORANDUM ORDER

I filed a final judgment in this case. (D.I. 193). Shortly thereafter, Defendant filed a motion to modify that judgment pursuant to Federal Rule of Civil Procedure 60(b). (D.I. 205). Subsequent briefing made clear that Defendant was primarily relying upon Rule 60(b)(5), which provides: "On motion and just terms, the court may relieve a party . . . from a final judgment, order, or proceeding for the following reasons: . . . (5) the judgment has been satisfied, released, or discharged; it is based on an earlier judgment that has been reversed or vacated; or applying it prospectively is no longer equitable." Plaintiffs oppose the motion. (D.I. 213).

The background to the pending motion is that Defendant filed an ANDA seeking to make and market a drug for two different methods of treatment—the IBS-D indication and the HE indication. I had a bench trial. After trial, I ruled in Defendant's favor on the IBS-D indication (as well as the composition claims), finding all patent claims asserted in relation to those two issues to be invalid. I ruled in Plaintiffs' favor only on the HE indication, finding all claims asserted in relation to that issue to be infringed and not invalid. In the final judgment, I ordered the FDA not to approve the ANDA before the latest expiration (in about 2029) of the patents on which Plaintiffs won. About a month after entry of the final judgment, Defendant filed an amended ANDA that purports to carve out everything relating to the HE indication. Defendant says, if the FDA approves the amended ANDA, Defendant would not be inducing infringement by marketing the pharmaceutical with the amended label. Other than providing the proposed label, Defendant has refused to provide any other information about the amended ANDA, including its status with the FDA or anything else.

I do not think Defendant's request fits in comfortably with the requirements of Rule 60(b)(5), and I do not think, even if it did, that it could be resolved in the summary fashion that Defendant seems to think it should be.

First, the Rule. Defendant says the judgment has been "satisfied," but I think it is pretty clear that the "satisfied, released, or discharged" language is talking about money, and is therefore inapplicable. Defendant says the injunction prohibiting FDA approval before

2029 is "no longer equitable" because Defendant no longer seeks to do the act that was the basis for the injunction. The case law says that Rule 60(b)(5) is for a significant change in circumstances. *See Rufo v. Inmates of Suffolk Cnty. Jail*, 502 U.S. 367, 383 (1992). While such a change in circumstances does not have to be entirely unforeseeable, a "modification should not be granted where a party relies upon events that actually were anticipated at the time" the final judgment was entered. *Id.* at 385. I do not think "changed circumstances" applies here. The case was tried as essentially three independent up-or-down decisions. In my experience with ANDAs, it is common, and certainly not rare, to have split decisions. ANDA practitioners and pharmaceutical companies surely know this. Thus, there were a limited number of possible outcomes at trial. But, of course, the trial results are not the changed circumstances, as the actual outcomes were previewed two weeks before the final judgment (D.I. 189) and disclosed at the same time as the final judgment. The only changed circumstance is that Defendant decided to amend its ANDA, which it filed on September 6, 2022 (D.I. 206 at 2), nearly one month after the final judgment. The changed circumstance is simply a voluntary decision of the trial loser to change course, which is neither unanticipated nor unforeseeable.

I also wonder about "equitableness" generally. Defendant made various strategic choices along the way, but now does not want to live with the consequences of those choices.[1] Defendant says that it is now worse

[1] I was assigned one related ANDA, where Defendant was only seeking approval to market the IBS-D indication, and not

off than other generics that settled with Plaintiffs and apparently can launch in 2028. While true, Defendant does not argue that it could not have settled and gotten the same deal as the other generics. Defendant says that it has gone to the effort of proving the asserted composition and IBS-D patent claims invalid, so other generics will be able to enter the market a lot sooner than 2028 by taking advantage of Defendant's accomplishments.[2] Defendant suggests this is inequitable (and perhaps it is), but the inequity does not exist between Plaintiffs and Defendant. To the extent there is inequity, it is between Defendant and other generics. Defendant says that the public will be harmed because Plaintiffs will not have any generic competition (with attendant lower costs) on the IBS-D treatment method for some period of time, even though Plaintiffs have no right to a monopoly on that treatment method. This is a bit speculative, since there is no information about if or when the FDA might approve the amended ANDA.

Second, the record. It 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.[3] Defendant, other than saying

---

the HE indication. *Salix Pharms., Ltd. v. Sun Pharms. Inds., LTD*, No. 19-734-RGA (D.Del. filed April 24, 2019). That Defendant quickly resolved its case with Plaintiffs.

[2] This may be a bit speculative too, because Plaintiffs have lots of relevant patents and patent claims, and, while presumably they advanced their best claims at the trial in this case, I would expect they have more listed in the Orange Book to assert against the next generic to file an ANDA.

[3] I had an ANDA trial in January 2023 where one of the issues is whether the carve out has been successful. The issue is hotly

it has successfully carved out the HE indication, and providing me the label, has presented no evidence in support of its assertion. Further, Rule 60(b) "does not allow relitigation of issues that have been resolved by the judgment." 11 WRIGHT, MILLER, & KANE, FEDERAL PRACTICE AND PROCEDURE § 2863, at 459 (3d ed. 2012). Defendant presents no facts indicating that it could not have litigated the carve-out or that it was denied a full and fair opportunity to do so. *Allergan, Inc. v. Sandoz Inc.*, 2013 WL 6253669, at *3 (E.D. Tex. Dec. 3, 2013), *aff'd*, 587 F. App'x 657 (Fed. Cir. 2014). As in *Allergan*, Defendant 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) that "is tantamount to seeking summary judgment premised on new allegations that only came to exist after the final judgment was rendered . . . ." *Id.*

Defendant states that Plaintiffs have not tried to state a claim against the carve out, and therefore, they cannot. I am unpersuaded that Plaintiffs have some duty now to state a claim on something that Defendant never raised as an issue before entry of final judgment. It is not surprising that Defendant has cited no case that requires a plaintiff to be able to state a claim on a new issue after judgment. What Defendant wants would essentially be a second litigation.

Third, the law. Plaintiffs say, and Defendant does not present any argument to the contrary, that what Defendant seeks is unprecedented in an ANDA case.

---

disputed. *See Sanofi-Aventis U.S. LLC v. Sandoz, Inc.*, No. 20-804-RGA, D.I. 355 at 2 (D.De1. Feb. 17, 2023) (arguing non-infringement because Sandoz removed certain information from its proposed label).

I am hesitant to be the first, because it just seems wrong to me that Defendant can litigate a case through trial and final judgment based on a particular ANDA, and then, after final judgment, change the ANDA to what it wishes it had started with, and win in a summary proceeding.

Thus, I DENY Defendant's Rule 60(b) motion. (D.I. 205).

IT IS SO ORDERED this 17th day of May, 2023.

/s/ RICHARD G. ANDREWS
United States District Judge

APPENDIX D

NOTE: This order is nonprecedential.

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.

Filed: June 13, 2024

ON PETITION FOR PANEL REHEARING AND REHEARING EN BANC

Before Moore, *Chief Judge*, Lourie, Dyk, Prost, Reyna, Taranto, Chen, Hughes, Stoll, and Cunningham, *Circuit Judges*.[1]

PER CURIAM.

O R D E R

Salix Pharmaceuticals, Ltd., Salix Pharmaceuticals, Inc., Bausch Health Ireland Ltd., and Alfasigma S.p.A filed a combined petition for panel rehearing and rehearing en banc.

Norwich Pharmaceuticals Inc. also filed a combined petition for panel rehearing and rehearing en banc.

The petitions were referred as petitions to the panel that heard the appeal, and thereafter the petitions were referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petitions for panel rehearing are denied.

The petitions for rehearing en banc are denied.

The mandate of the court will issue June 20, 2024.

FOR THE COURT

/s/ Jarrett B. Perlow
Jarrett B. Perlow
Clerk of Court

June 13, 2024
Date

[1] Circuit Judge Newman and Circuit Judge Stark did not participate.