NOTE: This disposition is nonprecedential.

United States Court of Appeals for the Federal Circuit

PHARMACYCLICS LLC, JANSSEN BIOTECH, INC.,
Plaintiffs-Appellees

v.

ALVOGEN, INC., NATCO PHARMA LIMITED,
Defendants-Appellants

2021-2270

Appeal from the United States District Court for the District of Delaware in No. 1:19-cv-00434-CFC-CJB, Chief Judge Colm F. Connolly.

Decided: November 15, 2022

CHRISTOPHER NEIL SIPES, Covington & Burling LLP, Washington, DC, argued for all plaintiffs-appellees. Plaintiff-appellee Pharmacyclics LLC also represented by ERICA NICOLE ANDERSEN, BRIANNE BHARKHDA.

IRENA ROYZMAN, Kramer Levin Naftalis & Frankel LLP, New York, NY, for plaintiff-appellee Janssen Biotech, Inc. Also represented by CHRISTINE WILLGOOS; HANNAH YUNKYUNG LEE, DANIEL DAVID WILLIAMS, Redwood Shores, CA.

SIEGMUND Y. GUTMAN, Proskauer Rose LLP, Los Angeles, CA, argued for defendants-appellants. Also represented by DAVID M. HANNA; JOHN E. ROBERTS, Boston, MA.

Before CHEN, BRYSON, and HUGHES, *Circuit Judges*.

BRYSON, *Circuit Judge*.

Appellees Pharmacyclics LLC and Janssen Biotech, Inc., (collectively, "Pharmacyclics") own several patents related to the compound ibrutinib, which is the active ingredient in Pharmacyclics' branded drug Imbruvica. Ibrutinib is one of a genus of compounds, known as "BTK inhibitors," that block the protein Bruton's tyrosine kinase ("BTK"). Imbruvica is used to treat a cancer of the immune system known as mantle cell lymphoma ("MCL"), including the "relapsed" or "refractory" type of MCL ("R/R MCL").[1]

In November 2018, appellants Alvogen, Inc., and Natco Pharma Limited (collectively, "Alvogen") filed an abbreviated new drug application ("ANDA") to market a generic version of Imbruvica. Pursuant to procedures set forth in the Hatch-Waxman Act, Pharmacyclics then brought this lawsuit charging Alvogen with infringement of a number of Pharmacyclics' patents relating to ibrutinib. The district court held a bench trial and determined that all of the asserted claims were infringed and not invalid. We affirm.

I

A

Pharmacyclics originally asserted dozens of claims across 17 patents, but by the time of trial, it had reduced the number of asserted claims to five: claim 10 of U.S.

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[1] R/R MCL is MCL that occurs in patients who have already received at least one prior therapy for MCL.

Patent No. 8,008,309 ("the '309 patent"), claim 2 of U.S. Patent No. 8,754,090 ("the '090 patent"), claim 5 of U.S. Patent No. 9,725,455 ("the '455 patent"), and claims 30 and 37 of U.S. Patent No. 9,655,857 ("the '857 patent").

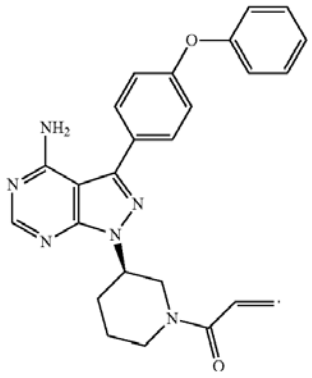
Claim 10 of the '309 patent recites the ibrutinib compound:

> 10. The compound of claim 1 [which claims a genus of BTK inhibitor compounds] having the formula 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one.

'309 patent, claim 10.

Claim 2 of the '090 patent, which depends from claim 1 of that patent, recites a method of treating MCL using ibrutinib at an oral dose of about 560 mg:

> 1. A method for treating mantle cell lymphoma in an individual who has already received at least one prior therapy for mantle cell lymphoma comprising administering to the individual once per day between about 420 mg to about 840 mg of an oral dose of an inhibitor of Bruton's tyrosine kinase (Btk) having the structure:



> 2. The method of claim 1, wherein the once per day oral dose is about 560 mg.

'090 patent, claims 1–2.

Claim 5 of the '455 patent, which depends from claim 1 of that patent, recites a crystalline form of ibrutinib:

> 1. A crystalline form A of [ibrutinib] that has an X-ray powder diffraction (XRPD) pattern comprising 2-Theta peaks at 5.7±0.1°, 18.9±0.1°, and 21.3±0.1°.
>
> 5. The crystalline form of claim 1, wherein the X-ray powder diffraction (XRPD) pattern further comprises 2-Theta peaks at 13.6±0.1°, 16.1±0.1°, and 21.6±0.1°.

'455 patent, claims 1, 5.

Claims 30 and 37 of the '857 patent recite tablet formulations for ibrutinib:

> 30. The high-load solid tablet formulation of claim 1 [which recites a genus tablet formulation for ibrutinib], consisting essentially of:
>
> a) about 70% w/w of ibrutinib,
> b) about 14% w/w of lactose monohydrate,
> c) about 5% w/w of microcrystalline cellulose,
> d) about 2% w/w of polyvinylpyrrolidone,
> e) about 7% w/w of croscarmellose sodium,
> f) about 1% w/w of sodium lauryl sulfate,
> g) about 0.5% w/w of colloidal silicon dioxide, and
> h) about 0.5% w/w of magnesium stearate.
>
> 37. The solid tablet formation of claim 27 [which recites a genus tablet formulation for ibrutinib in an amount of about 70 mg to about 840 mg] consisting essentially of

> a) about 69% w/w to about 71% w/w of ibrutinib,
> b) about 13% w/w to about 15% w/w of lactose monohydrate,
> c) about 2% w/w to about 5% w/w of microcrystalline cellulose,
> d) about 1% w/w to about 3% w/w of polyvinylpyrrolidone,
> e) about 6% w/w to about 8% w/w of croscarmellose sodium,
> f) about 1% w/w to about 4% w/w of sodium lauryl sulfate,
> g) about 0.4% w/w to about 0.6% w/w of colloidal silicon dioxide, and
> h) about 0.4% w/w to about 0.6% w/w of magnesium stearate.

'857 patent, claims 30, 37.

B

At trial, Alvogen stipulated that it infringed the asserted claims of the '309, '090, and '455 patents, and the district court found that Alvogen infringed the asserted claims of the '857 patent. *Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 385–86 (D. Del. 2021). Alvogen alleged that each of the asserted claims is invalid, based on various theories. The district court rejected each of those theories and held that none of the claims had been proved invalid by clear and convincing evidence. *See id.* at 424.

1

Alvogen argued that claim 10 of the '309 patent (the compound claim) was anticipated by an article referred to as "Pan." The parties did not dispute that the Pan article describes ibrutinib, but Pharmacyclics argued that the invention of claim 10 of the '309 patent pre-dated the publication of Pan. *Id.* at 390.

The Pan article was published on December 12, 2006, and the application for the '309 patent was filed on December 28, 2006. *Id.* However, Pharmacyclics argued that the date of invention of claim 10 was the date that one of two provisional patent applications was filed: either September 22, 2006, or October 6, 2006.[2] *Id.* Alvogen argued that the provisional applications did not establish priority because they did not satisfy the written description and enablement requirements of 35 U.S.C. § 112 with respect to the ibrutinib compound. *Id.* at 390–91. Therefore, Alvogen argued, the Pan article anticipated claim 10 of the '309 patent. *Id.*

The provisional applications disclosed ibrutinib and noted that the synthesis of ibrutinib "was accomplished using a procedure analogous to that described for" another compound, referred to as "[C]ompound 4." *See* J.A. 18001–02. The procedure described for Compound 4 begins with another compound, "[I]ntermediate 2." J.A. 16611, 18001. Alvogen argued that because the provisional applications did not disclose how to synthesize Intermediate 2, Compound 4 (and, by extension, ibrutinib) had not been enabled. *Pharmacyclics*, 556 F. Supp. 3d at 393.

The district court found that "the disclosure of the structure of Intermediate 2 in the Compound 4 Scheme would have enabled a skilled artisan to synthesize Intermediate 2." *Id.* at 394. The court based that finding on two considerations. First, the court observed that "[t]he provisional applications have a bracketed citation to the World Intellectual Property Organization patent WO 2001019829 ["WO '829"] immediately after they mention Intermediate 2." *Id.* at 393. The court found that "[a]n artisan of ordinary skill would have understood that the inventors cited [WO '829] to explain how to synthesize Intermediate 2." *Id.*

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[2] Those applications are U.S. Provisional Patent Application Nos. 60/826,720 and 60/828,590.

Second, and in the alternative, the district court found that "an artisan of ordinary skill could also have synthesized Intermediate 2 without the teachings of [WO '829] based on the structure of Intermediate 2 disclosed in the diagram of the Compound 4 Scheme." *Id.* In so finding, the court relied on testimony from Pharmacyclics' expert, Dr. Paul Reider, who testified that "his undergraduate students—whose abilities would fall below that of [an artisan of ordinary skill]—would have been able to synthesize Intermediate 2 . . . by working backwards from its structure to known starting compounds." *Id.* at 393–94.

Based on those findings, the district court concluded that the provisional applications contained adequate written description support for and sufficiently enabled claim 10 of the '309 patent. *Id.* at 398. Accordingly, the court concluded that claim 10 of the '309 patent was entitled to an invention date of September 22, 2006, and was not anticipated by the Pan article. *Id.*

2

Alvogen argued that claim 2 of the '090 patent (the method-of-treatment claim) was not adequately described or enabled, was obvious in view of four prior art references, and was invalid for obviousness-type double patenting. *Id.* at 398.

As for written description, the district court found that "ibrutinib is the only BTK inhibitor identified by name in the Summary of the Invention and is the only BTK [inhibitor] identified for the treatment of R/R MCL." *Id.* at 401. For those reasons, the court found that a skilled artisan would have recognized ibrutinib as "the inventor's preferred BTK inhibitor for treating R/R MCL." *Id.* The court then referred to "Example 13" in the written description, which discloses a protocol for a Phase II clinical trial involving the use of BTK inhibitors at a dose of 560 mg per day to treat R/R MCL. *Id.* (citing '090 patent, col. 141, line 58, through col. 142, line 27). The court found that

"[a]lthough Example 13 does not explicitly identify a specific BTK inhibitor to use," a skilled artisan "would understand to use the inventor's preferred BTK inhibitor (i.e., ibrutinib) in the Phase II protocol described in Example 13." *Id.* The court therefore concluded that Alvogen had not shown that claim 2 of the '090 patent was not adequately described. *Id.* at 407.

Alvogen's arguments on enablement largely mirrored its arguments on written description. The district court concluded that claim 2 had been enabled because "an artisan of ordinary skill would be able to follow the protocol of Example 13 using ibrutinib and thus practice the method described in claim 2." *Id.* at 406.

On the issue of obviousness, Alvogen proposed a combination of four prior art references: U.S. Patent Publication No. 2008/0076921 ("the '921 publication"); U.S. Patent No. 8,952,015 ("the '015 patent"); an article referred to as "Pollyea"; and a December 2009 press release. *Id.* at 401–02. Alvogen also sought to rely on another reference, "Advani," but the district court determined that Advani could not be considered part of Alvogen's obviousness combination and would instead be treated as background art. *Id.* at 402–03 n.7.

The '015 patent discloses ibrutinib by its chemical name, and it also discloses dozens of other compounds either by name or by structure.[3] '015 patent, col. 4, ll. 1–26; *id.* at col. 36, line 30 through col. 51, line 37. The written description of the '015 patent discloses a general dose range of "0.02–5000 mg per day" or "about 1–1500 mg per day" to

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[3] As the district court observed, the '921 publication and the '015 patent "share essentially the same written description and differ only in their claims." *Pharmacyclics*, 556 F. Supp. 3d at 401. Allusions to the '015 patent in this opinion therefore apply to both references.

treat a variety of conditions. *Id.* at col. 84, ll. 31–34. It adds that a "therapeutically effective amount[] may be determined by routine experimentation, including but not limited to a dose escalation clinical trial." *Id.* at col. 21, ll. 49–52. The '015 patent, however, does not specifically disclose using ibrutinib to treat R/R MCL. *Pharmacyclics*, 556 F. Supp. 3d at 401.

The Pollyea article reported the interim results of a Phase I dose escalation study of ibrutinib. The article disclosed dosing based on the patient's weight rather than using a fixed dose of about 560 mg per day. J.A. 16671. It further disclosed that none of the seven patients involved in the trial had exhibited complete or partial responses to treatment. *See* J.A. 16672. The December 2009 press release disclosed subsequent interim results for the Pollyea study and reported that two patients who suffered from had R/R MCL exhibited a partial response to the treatment. *See* J.A. 15041, 16451.

The district court found that a skilled artisan would not have been motivated to combine Alvogen's references to treat R/R MCL with a once-daily dose of about 560 mg of ibrutinib, for three reasons. First, the district court found that a skilled artisan would not have interpreted the results of the study disclosed in Pollyea "as showing that ibrutinib could be used as a treatment for R/R MCL," given the "unpredictable nature of oncology" and that only two R/R MCL patients in the study had exhibited any response to the treatment. *Pharmacyclics*, 556 F. Supp. 3d at 403. Second, the court found that none of the references, alone or in combination, would have motivated a skilled artisan to use a once-daily dose of about 560 mg. *Id.* That was because "[t]he only references that mention R/R MCL . . . disclose a weight-based dosing regimen," and the evidence did not suggest that conventional methods of determining an effective dose "would lead to a dose of about 560 mg." *Id.* Third, the court found that "safety concerns

about ibrutinib would have discouraged an artisan of ordinary skill from treating R/R MCL with ibrutinib." *Id.*

For similar reasons, the district court found that a skilled artisan would not have had a reasonable expectation of success in treating R/R MCL with a daily dose of about 560 mg of ibrutinib. *Id.* at 404. The court also found that six secondary considerations favored nonobviousness: a long-felt but unmet need, the failure of others, skepticism, unexpected results, praise, and commercial success. *Id.* at 404–06. The court therefore concluded that claim 2 of the '090 patent would not have been obvious because of the lack of a motivation to combine the references, the lack of a reasonable expectation of success, and the secondary considerations of nonobviousness. *Id.* at 407.

On the issue of obviousness-type double patenting, Alvogen argued that it was entitled to a presumption of obviousness because claim 20 of the '015 patent recites the administration of a "therapeutically effective amount" of ibrutinib, which the specification of that patent identified as falling within the range of 1 mg to 1500 mg. *Id.* at 407. The dosage recited in claim 2 of the '090 patent, about 560 mg, would fall within that range. *Id.*

The district court rejected Alvogen's presumption-of-obviousness argument for four reasons. First, the court noted that there were other differences, besides the dosage amount, between claim 20 of the '015 patent and claim 2 of the '090 patent. *Id.* at 408 (citing *Tris Pharma, Inc. v. Actavis Labs. FL, Inc.*, 503 F. Supp. 3d 183, 203 (D. Del. 2020)). Second, the court pointed out that the breadth of the ranges in the written description of the '015 patent weighed against applying the presumption of obviousness. *Id.* Third, the court restated its earlier finding that "routine experimentation would not have resulted in a dose amount of 560 mg." *Id.* at 409. And fourth, the court found that the evidence presented by Pharmacyclics at trial "would have rebutted any presumption of obviousness." *Id.*

3

Alvogen argued that claim 5 of the '455 patent (the crystalline form claim) was inherently anticipated by the clinical study disclosed in the Pollyea article and another reference, "Fowler," which disclosed updated results for the same study. *Id.* at 413. Alvogen also argued that the claim was obvious in view of a combination of four references. *Id.* at 412.

The written description of the '455 patent indicates that ibrutinib exists in multiple crystalline forms and in an amorphous form. '455 patent, col. 10, ll. 17–50. Claim 5 of the '455 patent recites one of those forms, "Form A," which is "the most stable form of ibrutinib currently known." *Pharmacyclics*, 556 F. Supp. 3d at 410.

On the issue of inherent anticipation, the study disclosed in the Pollyea and Fowler references used a BTK inhibitor known as PCI-32765. J.A. 16466, 16671. The district court found that PCI-32765 refers to ibrutinib generally, and not to any specific form of ibrutinib. *Pharmacyclics*, 556 F. Supp. 3d at 410. But the evidence presented at trial showed that every lot of PCI-32765 used in the study was Form A of ibrutinib. *See* Appellants' Br. 34–35.

The district court concluded that Alvogen had not proved that the study disclosed in Pollyea and Fowler "could only be conducted with crystalline Form A of ibrutinib." *Pharmacyclics*, 556 F. Supp. 3d at 414. The court added that "a skilled artisan, reviewing Pollyea or Fowler, would not have necessarily recognized that Pollyea's or Fowler's authors used crystalline Form A for their reported clinical study." *Id.* (citing *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1382 (Fed. Cir. 2018)) (cleaned up). Accordingly, the court determined that claim 5 of the '455 patent was not inherently anticipated by the study disclosed in Pollyea and Fowler. *See id.*

On the issue of obviousness, Alvogen argued that claim 5 of the '455 patent would have been obvious in view of the following four references: an article referred to as "Honigberg"; U.S. Patent No. 7,514,444 ("the '444 patent"); and two general references addressing polymorphism, "Miller" and "Bauer."[4] *Id.* at 410–11.

The Honigberg reference discloses the chemical structure of ibrutinib and notes that ibrutinib had "shown promising clinical activity" as a "potent, selective and irreversible [BTK] inhibitor." J.A. 16472. Similarly, the '444 patent discloses the chemical name and structure of ibrutinib, along with other compounds, as well as a method for synthesizing ibrutinib. '444 patent, col. 4, ll. 4–6; *id.* at col. 97, ll. 1–35. The patent further states that the disclosed compounds "may be in various forms," including crystalline forms, but does not assert that any crystalline forms of ibrutinib actually exist. *Id.* at col. 60, ll. 38–49.

The Miller and Bauer references are general references on polymorphism. Neither mentions ibrutinib or teaches how to make a crystalline form of ibrutinib. *See generally* J.A. 17837–93 (Miller); J.A. 17401–09 (Bauer). Miller "gives a general introduction to crystal forms, crystal stability, crystallization, and polymorph screening." *Pharmacyclics*, 556 F. Supp. 3d at 411. Bauer teaches that "crystalline solids are usually highly stable" but that the polymorphs of a particular drug that will form under certain conditions "cannot be predicted." *Id.* (citing J.A. 17402).

The district court found that a skilled artisan "would have been motivated to develop *a* crystalline form of

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[4] "Polymorphism" refers to a compound having more than one crystalline form. *Pharmacyclics*, 556 F. Supp. 3d at 409. The crystalline forms of such a compound are referred to as "polymorphs." *Id.*

ibrutinib" based on the four references identified by Alvogen, but that none of those references "would have motivated an artisan to develop a crystalline form of ibrutinib with the claimed 2-Theta peaks," i.e., Form A. *Id.* at 412. That was because none of the references disclosed such a crystalline form or "suggested that [Form A] would be more desirable than any other crystalline form." *Id.*

The district court similarly found that a skilled artisan "could not reasonably have expected to make a crystalline form of ibrutinib with the six claimed 2-Theta peaks." *Id.* The court based that finding on the fact that "discovering new crystalline forms is challenging and unpredictable," and that the prior art did not teach which of "numerous variables in the crystallization process" would have been "key to crystallizing ibrutinib." *Id.* The court also found that two secondary considerations weighed in favor of nonobviousness: unexpected benefits and copying. *Id.* at 412–13.

In view of its findings regarding the motivation to combine, the reasonable expectation of success, and the secondary considerations, the court concluded that claim 5 of the '455 patent would not have been obvious. *Id.* at 414.

4

Alvogen argued that claims 30 and 37 of the '857 patent (the tablet formulation claims) were invalid for lack of adequate written description and obviousness. *Id.*

The district court observed that the written description of the '857 patent "recites verbatim the formulations claimed in claims 30 and 37." *Id.* at 415 (citing '857 patent, col. 43, line 47 through col. 44, line 6). Second, the court noted that the specification discloses an ibrutinib tablet formulation, BK21A, which satisfies the limitations of claims 30 and 37. *Id.* at 416 (citing '857 patent at Table 1F). Third, the court noted that the specification describes experiments conducted using the BK21A formulation at

doses of 140 mg and 560 mg. *Id.* (citing '857 patent at Tables 7, 8). In view of those disclosures, the court found that a skilled artisan could have scaled the formulations disclosed in the '857 patent "to make a tablet with the full range of claimed ibrutinib amounts." *Id.* Accordingly, the court concluded that claims 30 and 37 were not invalid for lack of adequate written description. *Id.* at 424.

On the issue of obviousness, the district court concluded that claims 30 and 37 would not have been obvious in view of Alvogen's proposed combination of references. *Id.* at 423–24. That ruling is not at issue in this appeal.

II

Alvogen challenges several of the district court's determinations. First, Alvogen argues that the court erred in rejecting Alvogen's written description and obviousness challenges to claim 2 of the '090 patent. Second, Alvogen argues that the court erred in concluding that claim 5 of the '455 patent was neither inherently anticipated nor obvious. Third, Alvogen argues that the court erred in rejecting Alvogen's written description challenges to claims 30 and 37 of the '857 patent. Fourth, Alvogen argues that the court erred in concluding that claim 10 of the '309 patent was not anticipated by the Pan reference. We reject each of Alvogen's arguments.

On appeal from a bench trial, we review the district court's legal conclusions de novo and the district court's factual findings for clear error. *UCB, Inc. v. Watson Lab'ys Inc.*, 927 F.3d 1272, 1286 (Fed. Cir. 2019). The clear error standard requires courts to affirm the finding below unless we have a "definite and firm conviction that a mistake has been made." *Biogen Int'l GMBH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1341 (Fed. Cir. 2021) (citation omitted). Anticipation and written description are issues of fact. *Id.*; *UCB*, 927 F.3d at 1286. We review the legal conclusion of obviousness de novo and any underlying factual findings for clear error. *UCB*, 927 F.3d at 1286.

A

Alvogen first argues that the district court erred in determining that claim 2 of the '090 patent contained adequate written description support, was enabled, and would not have been obvious.

1

The specification of the '090 patent discloses two clinical trial protocols relating to treating R/R MCL with a BTK inhibitor. One protocol, "Example 7," discloses treating R/R MCL using a genus of BTK inhibitors dosed based on a patient's weight. '090 patent, col. 133, ll. 42–55. The other, "Example 13," discloses treating R/R MCL using a broader genus of BTK inhibitors at a dose of 560 mg per day. *Id.* at col. 141, line 58 through col. 142, line 7. The summary of the invention section of the '090 patent further discloses treating R/R MCL with ibrutinib. *Id.* at col. 4, ll. 59–67. Alvogen argues that the district court "cherry-pick[ed]" those aspects of the specification in finding that there was written description support for claim 2. Appellants' Br. 16.

The written description requirement is satisfied if the specification conveys with reasonable clarity to those skilled in the art that the inventor was in possession of the claimed invention. *Biogen*, 18 F.4th at 1341–42. When a specification discloses its subject matter in terms of a broad genus, we have required that the specification "provide sufficient 'blaze marks' to guide a reader through the forest of disclosed possibilities" toward the claimed invention. *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1346 (Fed. Cir. 2013) (quoting *In re Ruschig*, 379 F.2d 990, 994–95 (C.C.P.A. 1967)).

Alvogen argues that the specification of the '090 patent did not contain sufficient blaze marks, because a skilled artisan would not have understood ibrutinib to be the inventor's preferred BTK inhibitor. As the district court

observed, however, "ibrutinib is the only BTK inhibitor identified by name in the Summary of the Invention and is the only BTK [inhibitor] identified for the treatment of R/R MCL" in the '090 patent. *Pharmacyclics*, 556 F. Supp. 3d at 401. In view of those disclosures, we hold that it was not clearly erroneous for the district court to find that the '090 patent demonstrated that ibrutinib was the inventor's preferred BTK inhibitor.

Alvogen also argues that the protocol disclosed in Example 13, which describes treating R/R MCL with a genus of BTK inhibitors at a dose of 560 mg per day, does not describe the full claimed scope of "about 560 mg." That argument is unpersuasive in view of the fact that the summary of the invention explicitly discloses one possible dosage of ibrutinib to be "about 560 mg/day." '090 patent, col. 5, ll. 8–11.

This case is unlike our recent decision in *Biogen*, in which we upheld a district court's ruling that a method-of-treatment claim lacked adequate written description support. *Biogen*, 18 F.4th at 1342–45. In that case, the claimed dosage of 480 mg was "listed only once in the entire specification," and it appeared "at the end of one range among a series of ranges." *Id.* at 1343. By contrast, the dosage of "about 560 mg/day" recited in claim 2 of the '090 patent is expressly recited by itself (rather than as part of a range) in the specification, and a 560 mg daily dose appears again in the specification's discussion of Example 13. Moreover, our standard of review is significant; in *Biogen*, we held that the district court did not clearly err when it found that the claim lacked written description support. 18 F.4th at 1346. In this case, the court found the opposite: that claim 2 was adequately described by the specification.

Viewing the written description of the '090 patent in its entirety, we hold that the district court did not clearly err in finding that claim 2 of the '090 was adequately supported by the written description.

2

Alvogen's argument on the issue of enablement is similar to its argument on written description. Specifically, Alvogen argues that the specification does not teach a skilled artisan how to practice claim 2 without undue experimentation.

The crux of Alvogen's argument is that Example 13 discloses a dose of exactly 560 mg per day, rather than the full claimed scope of "about" 560 mg per day. However, the summary of the invention explicitly discloses a dose of "about 560 mg/day." '090 patent, col. 5, ll. 8–11. With respect to enablement, the district court concluded that a skilled artisan "would be able to follow the protocol of Example 13 using ibrutinib and thus practice the method described in claim 2." *Pharmacyclics*, 556 F. Supp. 3d at 406. We discern no error in that conclusion.

3

As to the obviousness of claim 2 of the '090 patent, Alvogen first challenges the district court's finding that a skilled artisan would not have been motivated to treat R/R MCL with ibrutinib. Alvogen argues that "when claim 20 of the '015 patent discloses treating MCL with ibrutinib," it necessarily discloses the treatment of R/R MCL. Appellant's Br. 23. That argument runs headlong into the district court's factual finding that "a disclosure of treating MCL with a drug" would not be interpreted by a skilled artisan "as evidence that the drug would be effective at treating R/R MCL." *Pharmacyclics*, 556 F. Supp. 3d at 403 n.8.

Alvogen also argues that the district court improperly discounted the disclosure in the December 2009 press release that two R/R MCL patients had exhibited a partial response to ibrutinib. But given the small sample size, we are not persuaded that the district court clearly erred in finding that a skilled artisan "would not interpret th[o]se results as showing that ibrutinib could be used as a

treatment for R/R MCL," particularly in view of the fact that "less than five percent of oncology drugs that enter a Phase I trial ultimately receive FDA approval." *Id.* at 403.[5]

Alvogen also argues that the district court failed to properly account for the admission in the '015 patent that a "therapeutically effective amount" of ibrutinib could be determined using "routine experimentation." *See* '015 patent, col. 21, ll. 49–52. The district court found, however, that a "typical 3+3 dose escalation study . . . would have reached the [maximum tolerated dose] as the dosage," which for ibrutinib is "above 560 mg." *Pharmacyclics*, 556 F. Supp. 3d at 403. The district court further found that "[t]o reach the claimed dose of about 560 mg, an artisan would need to conduct a study using pharmacodynamic endpoints," which Alvogen's combination of references did not disclose. *Id.* Although Alvogen suggests that "other routine methods could achieve the same claimed dose," it offers no evidence of what such a routine method would be. *See* Appellants' Br. 28. We discern no error in the district court's findings on that issue, and we therefore hold that the district court did not clearly err in determining that the prior art would not have motivated a skilled artisan to use a dose of about 560 mg per day.

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[5] Relatedly, Alvogen argues that the district court erred by failing to require a demonstration of efficacy for purposes of written description and enablement but "imposing an efficacy requirement for obviousness." Appellants' Br. 27. The court imposed no such requirement for obviousness. Alvogen argued to the district court that a skilled artisan would be motivated to combine Pollyea and the press release with the '015 patent because the data from the Pollyea study "show[ed] that ibrutinib is efficacious in treating R/R MCL." J.A. 12350. The court merely rejected that argument, and it did not err in doing so.

Further as to the motivation to combine, Alvogen argues that the district court erred in relying on the testimony of Dr. Reider regarding safety concerns involving ibrutinib. According to Alvogen, Dr. Reider's testimony focuses on safety concerns as of 2006, whereas the obviousness of claim 2 should be measured from 2010. Alvogen ignores that the district court also relied on testimony from another expert, Dr. Simon Rule, in finding that "[a]n artisan of ordinary skill would not have considered irreversible BTK inhibitors or molecules with a Michael acceptor [which were considered to be dangerous] to be promising drug classes in June 2010." *Id.* at 399 (citing J.A. 15002, 15050). Alvogen's only evidence that a skilled artisan would have considered ibrutinib to be safe as of 2010 is the set of references relating to the clinical trial described in Pollyea. *See* Appellants' Br. 28–29. We do not find that those references demonstrate that the district court clearly erred in finding that safety concerns weighed against a motivation to combine.

Alvogen next argues that the district court erred in not applying the presumption of obviousness that Alvogen argues was created by claim 20 of the '015 patent. We reject that argument for two reasons.

First, a presumption of obviousness may be invoked "when the only difference from the prior art is a difference in the range or value of a particular variable." *In re Kumar*, 418 F.3d 1361, 1366 (Fed. Cir. 2005). In this case, however, there are additional differences between the prior art and claim 2 of the '090 patent. For example, the district court found that the prior art did not disclose that ibrutinib was effective at treating R/R MCL in particular. *Pharmacyclics*, 556 F. Supp. 3d at 403 & n.8. That finding was not clearly erroneous.

Second, the district court found that Pharmacyclics nevertheless "would have rebutted any presumption of

obviousness." *Id.* at 409. Alvogen has not persuaded us that the court clearly erred in making that finding.

Regarding the secondary considerations cited by the district court, we need not reach that issue because the court's findings regarding the motivation to combine and reasonable expectation of success are "fatal to Alvogen's obviousness theory." *Id.* at 407. We hold that the court did not err in concluding that claim 2 of the '090 patent would not have been obvious, and we therefore affirm the court's judgment with respect to that claim.

B

Alvogen next argues that the district court erred in determining that claim 5 of the '455 patent was not inherently anticipated and would not have been obvious.

1

In Alvogen's view, the fact that Form A was the only form of ibrutinib actually used in the clinical study disclosed in Pollyea and Fowler was sufficient to inherently anticipate claim 5 of the '455 patent, even if another form of ibrutinib could have been used in the clinical study.

In support of its argument, Alvogen relies upon our decision in *Abbott Laboratories v. Geneva Pharmaceuticals, Inc.*, 182 F.3d 1315 (Fed. Cir. 1999). In that case, we held that the sale of a compound, which was later determined to be in the same form as that recited in the asserted claim, triggered the on-sale bar even though "at the time of the sales, the parties to the . . . transactions did not know the identity of the particular crystalline form with which they were dealing." *Id.* at 1317–18. As the *Abbott* court noted, however, the key question with respect to the on-sale bar is what the product that was sold actually embodied. *See id.* at 1319. Once it became clear that the sold product contained the same components that were listed in the claims, that was enough to support a finding of invalidity. *See id.* When determining whether a claim is inherently

anticipated by a prior art publication, however, the question is different: The question is what is "necessarily" inherent in the anticipating reference. *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003).

Our decision in *Endo Pharmaceuticals*, a case on which the district court relied, is closely analogous to this case. In *Endo*, the defendant relied on prior art publications that reported on a clinical study for testosterone therapy delivered by injection. *Endo*, 894 F.3d at 1376. The claim at issue required a specific "vehicle formulation" for the injection, and it was later revealed that the vehicle formulation used in the clinical study was the same as that recited in the claim. *Id.* at 1381. The *Endo* court noted that there was no evidence "that only one vehicle formulation—the claimed vehicle formulation" could be used to achieve the results of the clinical study disclosed in the publications. The court therefore found no error in the trial court's finding that the claimed vehicle formulation was not inherent in the prior art. *Id.* at 1381–83.

In this case, the district court likewise found no evidence that only Form A could have been used to achieve the results of the clinical study disclosed in Pollyea and Fowler. To the contrary, the court found that "a Phase I dose escalation study could be performed with amorphous ibrutinib or one of its metastable polymorphs," and therefore that "Form A was not necessarily present in Pollyea or Fowler." *Pharmacyclics*, 556 F. Supp. at 414. The court's findings on that score were not clearly erroneous, and in light of *Endo*, those findings dictate rejection of Alvogen's inherent anticipation argument.

2

On the issue of obviousness, the district court found that a skilled artisan would not have been motivated to combine Honigberg, the '444 patent, Miller, and Bauer to make Form A of ibrutinib, and would not have had a reasonable expectation of success in doing so. Alvogen

challenges those findings as well as the court's findings regarding the secondary considerations of nonobviousness.

Neither party disputes the district court's finding that "an artisan of ordinary skill would have been motivated to develop *a* crystalline form of ibrutinib." *See id.* at 412. Alvogen argues, however, that the court should have found that a skilled artisan would have been motivated to develop the most stable form of ibrutinib, which is now known to be Form A, and that the skilled artisan would have had a reasonable expectation of successfully developing Form A.

In support of those arguments, Alvogen cites the expert opinion of Dr. Jennifer Swift, who testified that a skilled artisan would have inevitably developed Form A upon performing a routine polymorph screen. J.A. 14166. Alvogen adds that the Miller reference "demonstrates that a [skilled artisan] would have designed a routine polymorph screen to discover the most stable form as soon as possible in the screen." Appellants' Br. 44 (citing J.A. 17862).

Relying on contrary testimony, the district court found that "[d]iscovering new crystalline forms is challenging and unpredictable." *Pharmacyclics*, 556 F. Supp. 3d at 410. For example, Dr. Allan Myerson, Pharmacyclics' expert, testified that a skilled artisan would not "have been able to predict in advance whether a new compound would form polymorphs," and that polymorphs can be discovered outside the context of a polymorph screen. J.A. 15326–27. Dr. Myerson added that "we also can't predict in advance the physical properties that a crystalline form will have." J.A. 15418. Dr. John Steed, the expert for one of Alvogen's codefendants, testified similarly. *See* J.A. 14325–28. In view of the testimony of Drs. Myerson and Steed, the district court's finding of no reasonable expectation of success cannot be deemed clearly erroneous.

We disagree with Alvogen's contention that the district court's findings required a skilled artisan to "predict[]" what conditions would result in the production of Form A

of ibrutinib. Appellants' Br. 47. Rather, the court found that, given the lack of teaching in the art regarding crystalline forms of ibrutinib and the expert testimony that polymorph screening can produce unpredictable results, a skilled artisan would not have reasonably expected success in producing Form A of ibrutinib. That finding was not clearly erroneous. *See Grunenthal GMBH v. Alkem Lab'ys Ltd.*, 919 F.3d 1333, 1344 (Fed. Cir. 2019) (upholding a district court's finding that a skilled artisan would not have expected success in producing a particular crystalline form of a compound when a skilled artisan would not have had "reason to know[] how the multiple variables involved in conducting a polymorph screen would affect the recrystallization" of the compound).

Because we hold that the district court did not err in finding that a skilled artisan would not have been motivated to combine the prior art to create Form A and would not have had a reasonable expectation of success in doing so, we need not reach Alvogen's arguments regarding the secondary considerations of nonobviousness. We affirm the district court's determination that claim 5 of the '455 patent is neither inherently anticipated nor obvious.

C

Alvogen next argues that the district court erred in finding that claims 30 and 37 of the '857 patent were adequately supported by the written description.

Alvogen points to BK21A, a formulation that is disclosed in the specification and that embodiesis one species of the ranges recited in claims 30 and 37. *See* '857 patent, col. 89, ll. 43–54. Alvogen argues that possession of that one species is not sufficient to demonstrate possession of the broader ranges recited in claims 30 and 37.

The problem for Alvogen, however, is that the precise ranges recited in the claims are found in formulations disclosed in the specification. *Id.* at col. 43, line 64, through

col. 44, line 6 (claim 30); *id.* at col. 43, ll. 47–63 (claim 37). The specification also discloses that the dosage of ibrutinib can range from "about 35 mg to about 840 mg per tablet." *Id.* at col. 45, ll. 32–34. Because the written description describes the ingredient amounts "by their respective weight concentrations," and because the written description describes experiments conducted using BK21A at two different doses of ibrutinib, the district court found that the written description "would have conveyed to [a skilled artisan] that the inventor had possession of the claimed subject matter." *Pharmacyclics*, 556 F. Supp. 3d at 416. That finding is not clearly erroneous, and we therefore affirm the district court's judgment with respect to claims 30 and 37 of the '857 patent.[6]

D

Alvogen's final challenge is to the district court's finding that the Pan reference did not anticipate claim 10 of the '309 patent. Alvogen argues that a skilled artisan could not have synthesized Intermediate 2 without undue experimentation, and that the court failed to apply the proper legal standard for incorporation of a document by reference.

On the first point, Alvogen argues that it was error for the district court to rely upon the testimony of Dr. Reider in finding that the provisional applications enabled

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[6] We reject Alvogen's argument that the district court "read into the specification [the] supposed knowledge of a [skilled artisan]" that the amounts disclosed with respect to BK21A could be scaled. Appellants' Br. 55. The use of weight concentrations in describing BK21A and in claims 30 and 37, along with the use of two different doses of the BK21A tablet, are sufficient to convey that the tablet formulation can be scaled without importing any extraneous knowledge of a skilled artisan.

Intermediate 2. Specifically, Alvogen argues that Dr. Reider's testimony that his undergraduate students could synthesize intermediate 2 did not establish that they could do so "without undue experimentation." Appellants' Br. 60–62. Alvogen also points to our holding in *Genentech, Inc. v. Novo Nordisk A/S* that "the specification, not the knowledge of one skilled in the art, . . . must supply the novel aspects of an invention in order to constitute adequate enablement." 108 F.3d 1361, 1366 (Fed. Cir. 1997).

We hold that it was not error for the district court to rely on the testimony of Dr. Reider. Although Dr. Reider did not explicitly state that his students could have synthesized ibrutinib without undue experimentation, his testimony clearly conveyed that was the case. *See* J.A. 15108–10. Moreover, it is clear that Intermediate 2 was not novel because it was disclosed in the WO '829 publication. *Pharmacyclics*, 556 F. Supp. 3d at 398. The district court therefore did not run afoul of our holding in *Genentech,* because Intermediate 2 was not a "novel aspect[]" of claim 10 of the '309 patent. *See Genentech*, 108 F.3d at 1366.

On the second point, Alvogen argues that the district court erred in determining that the provisional applications had incorporated the WO '829 publication by reference. That argument is not dispositive, because the court properly found that "a skilled artisan could have synthesized Intermediate 2 and thus ibrutinib" without reference to WO '829. *Pharmacyclics*, 556 F. Supp. 3d at 397–98. In any event, formal incorporation by reference is not necessary if the material being incorporated is background art. *See, e.g.*, *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006) (holding that information readily accessible in journals need not be incorporated by reference in order to enable the patent claims at issue). Accordingly, we find Alvogen's argument as to incorporation by reference to be unpersuasive. We therefore affirm the district court's ruling that claim 10 of the '309 patent is not anticipated by the Pan article.

* * * * *

Finding no reversible error in any of the rulings of the district court challenged on appeal, we uphold the judgment of the district court.

AFFIRMED