IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PHARMACYCLICS LLC and JANSSEN BIOTECH, INC., Plaintiffs, v. ALVOGEN PINE BROOK LLC and NATCO PHARMA LTD., Defendants.	Civil Action No. 19-0434-CFC-CJB

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MEMORANDUM OPINION

August 19, 2021
Wilmington, Delaware

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COLM F. CONNOLLY
CHIEF JUDGE

Plaintiffs Pharmacyclics LLC and Janssen Biotech, Inc. (collectively Pharmacyclics) have sued Defendants Alvogen Pine Brook LLC and Natco Pharma Ltd. (collectively Alvogen) pursuant to the Hatch Waxman Act, 21 U.S.C. § 355(j), for infringement of four patents: U.S. Patent Nos. 8,008,309 (the #309 patent), 8,754,090 (the #090 patent), 9,655,857 (the #857 patent), and 9,725,455 (the #455 patent). Pharmacyclics listed the asserted patents in the so-called Orange Book administered by the U.S. Food & Drug Administration (FDA) to cover Pharmacyclics' brand-name drug Imbruvica®. This case arises out of Alvogen's submission to the FDA of an Abbreviated New Drug Application (ANDA) for approval to market generic versions of Imbruvica® tablets. Section 271(e)(2)(A) of the Patent Act, 35 U.S.C. § 1 *et seq.*, defines the filing of an ANDA as an act of infringement. *See Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1325 (Fed. Cir. 2012).

I. BACKGROUND

Imbruvica® is used to treat patients with small cell lymphomas in adults. Imbruvica® is presently available in capsules in 70 mg and 140 mg strengths, and in tablets in 140 mg, 280 mg, 420 mg, and 560 mg strengths. Imbruvica® works because its active ingredient—ibrutinib—disrupts the protein known as Bruton's

tyrosine kinase (BTK), which is thought to play a role in unregulated cell reproduction. Because it interrupts BTK, ibrutinib belongs to a class of molecules referred to as BTK inhibitors.

The asserted patents cover various aspects of Imbruvica®. The #309 patent's claims are generally directed to the ibrutinib molecule. The #090 patent's claims are generally directed to methods of treating a specific small cell lymphoma called relapsed or refractory mantle cell lymphoma. The #455 patent's claims are generally directed toward a crystalline form of ibrutinib. The #857 patent's claims are generally directed to formulations of tablets containing ibrutinib. Each of the asserted patents is listed in the FDA's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) for Imbruvica®. Janssen is the exclusive licensee of each patent. JTX-148 at 35; Tr. 1899:9–17.

Alvogen submitted ANDA No. 212763 seeking FDA approval to manufacture and sell ibrutinib tablets in 140 mg, 280 mg, 420 mg, and 560 mg strengths. Alvogen's ANDA contains a so-called Paragraph IV certification stating that certain patents listed in the Orange Book for Imbruvica® tablets are invalid, not infringed by its proposed ANDA product, or both. Pharmacyclics brought this infringement action based on the Paragraph IV certification. It has asserted claim 10 of the #309 patent, claim 2 of the #090 patent, claim 5 of the #455 patent, and claims 30 and 37 of the #857 patent.

Alvogen has stipulated that its ANDA product infringes the asserted claims of the #309 patent, #090 patent, and #455 patent under my claim constructions. D.I. 295. I ruled at trial that Alvogen infringes the asserted claims of the #857 patent. Tr. 1976:8–1977:6, 1978:12–19, 1980:19–24. Alvogen offers numerous invalidity theories for the patents asserted against it. It argues that claim 10 of the #309 patent is anticipated.[1] It argues that claim 2 of the #090 patent lacks written description, is not enabling, is obvious, and is an obvious variant of an already patented invention (obviousness-type double patenting). It argues that claim 5 of the #455 patent is anticipated and obvious. And finally, it argues that claims 30 and 37 of the #857 patent are obvious and lack written description.

In October 2020, I held a seven-day bench trial. That trial also included defendants from a related action that settled posttrial. The parties submitted posttrial briefing and proposed findings of fact. As required by Federal Rule of Civil Procedure 52(a)(1), I have set forth separately below my findings of fact and conclusions of law.

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[1] Alvogen did not pursue posttrial its earlier arguments that claim 10 is invalid for obviousness, lack of enablement, and lack of written description. *See* Tr. 380:24–381:5, 400:21–23, 480:5–22; Tr. of Hr'g Oct. 29, 2020 at 23:7–14.

II. LEGAL STANDARDS

A. Obviousness

Under § 103 of the Patent Act,[2] a patent "may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103 (2006). As the Supreme Court explained in the seminal case *Graham v. John Deere Co.*, 383 U.S. 1 (1966), under § 103, "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." *Id.* at 14. Section 103 ensures that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). "Were it otherwise

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[2] Congress amended the Patent Act in 2011 when it enacted the Leahy-Smith America Invents Act (AIA). *See* Pub. L. No. 112-29, 125 Stat. 284, 296 (2011). The parties agree that pre-AIA law applies to the #309, #090, and #457 patents and that AIA law applies to the #857 patent. Alvogen contends that claims 30 and 37 of the #857 patent are invalid for obviousness under 35 U.S.C. § 103 and for lacking adequate written description under 35 U.S.C. § 112. Because the AIA versions of these sections of the Act do not differ from the pre-AIA versions in any respect relevant to the issues before me, for simplicity I will cite only to the pre-AIA Act.

patents might stifle, rather than promote, the progress of useful arts." *Id.* (citing U.S. Const. art. I, § 8, cl. 8).

The Court reaffirmed in *KSR* that the "framework" set out in the following paragraph from *Graham* governs the application of § 103, *id.* at 406:

> While the ultimate question of patent validity is one of law, the [§] 103 condition [of patentability] . . . lends itself to several basic factual inquiries. Under [§] 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham, 383 U.S. at 14–15 (citations omitted).

It is clear that under this framework, a district court must consider in an obviousness inquiry the three primary factors identified by the Court in *Graham*: (1) the scope and content of the prior art, (2) the differences between the prior art and the claims at issue, and (3) the level of ordinary skill in the pertinent art. Less clear is the role, if any, secondary considerations should play in the analysis.

The logical—some would say necessary—implication of the Court's use of the word "secondary" in *Graham* and its holding that the secondary considerations "might be utilized" and "may have relevancy" is that a district court is permitted—

but not required in all cases—to examine such considerations in evaluating an obviousness-based invalidity challenge. The Court seemed to confirm as much in *KSR*, when it noted that "*Graham* set forth a broad inquiry and *invited* courts, where appropriate, to look at any secondary considerations that would prove instructive." *KSR*, 550 U.S. at 415 (emphasis added).

But a district court ignores *Graham*'s "invitation" to examine secondary considerations at its peril. One legal scholar, Harmon, has observed that under Federal Circuit law "[w]e are able now safely to strike the 'may' in the . . . sentence" in *Graham* in which the Court stated that secondary "indicia of obviousness and nonobviousness . . . may have relevancy." Robert Harmon, Cynthia Homan, Laura Lydigsen, *Patents and the Federal Circuit* 245 (13th ed. 2017). Harmon correctly notes that "[t]he Federal Circuit has emphatically and repeatedly held that objective evidence of non-obviousness must be taken into account always and not just when the decisionmaker is in doubt." *Id.* In *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983), for example, the Federal Circuit held that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Id.* at 1538. And in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063 (Fed. Cir. 2012), the Federal Circuit reaffirmed that holding, *id.* at 1079, and went on to

say that the Supreme Court in *Graham* "did not relegate . . . to 'secondary status'" the "objective factors" the Supreme Court had explicitly identified in *Graham* as "secondary considerations," *id.* at 1078.

It is true that less than a month after *In re Cyclobenzaprine*, a different Federal Circuit panel held in *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012) that because it found that the defendants had "failed to prove that [the challenged patent claim] would have been *prima facie* obvious over the asserted prior art," it "need not address" the "objective evidence" of commercial success, long-felt need, and the failure of others. *Id.* at 1296. But the safer course for a district court faced with an obviousness challenge is to treat *Graham*'s invitation to look at secondary considerations like a subpoena.

Obviousness is assessed based on the perspective of an artisan of ordinary skill at the time of the invention. *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). The court therefore needs to guard against "hindsight bias" that infers from the inventor's success in making the patented invention that the invention was obvious. *In re Cyclobenzaprine*, 676 F.3d at 1079. The ultimate question in the obviousness analysis is "whether there was an apparent reason [for an artisan of ordinary skill] to combine [at the time of the invention] the known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. "The analysis is objective." *Id.* at 406. Thus, a court must determine whether an

artisan of ordinary skill "would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success [in] doing so." *In re Cyclobenzaprine*, 676 F.3d at 1069.

The party challenging the patent's validity bears the burden of proving obviousness by clear and convincing evidence. *Id.* at 1068–69. In weighing the *Graham* factors to decide whether the party has met that burden, the district court must be guided by common sense. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1238 (Fed. Cir. 2010). Indeed, "the legal determination of obviousness may include recourse to logic, judgment, and common sense, in lieu of expert testimony." *Id.* at 1239. In *KSR*, the Supreme Court warned lower courts to avoid "[r]igid preventative rules that deny factfinders common sense" and to employ instead "an expansive and flexible approach" under the *Graham* framework. *KSR*, 550 U.S. at 415, 421. Thus, the district court may "reorder[ ] in any particular case" the "sequence" in which it considers the *Graham* factors. *Id.* at 407. And although a court should consider carefully the published prior art, "[t]he obviousness analysis cannot be confined by . . . overemphasis on the importance of published articles and the explicit content of issued patents." *Id.* at 419.

"[A]ny need or problem known in the field of endeavor at the time of the invention and addressed by the patent can provide a reason for combining the

elements in the manner claimed." *Id.* at 420. And "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[T]he fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* at 421. But a combination is obvious to try only "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions" in the prior art at the time of the invention. *Id.* And the court must also be mindful that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 416.

B. Obviousness-Type Double Patenting

The doctrine of double patenting prohibits a person from obtaining claims in a patent that are not patentably distinct from claims in a patent issued earlier to the same person. *AbbVie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1373 (Fed. Cir. 2014) ("[The doctrine] is designed to prevent an inventor from securing a second, later expiring patent for the same invention."); *Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1212 (Fed. Cir. 2014) (doctrine prohibits "obvious modifications of [an] invention that are not patentably distinct improvements"). Double patenting arguments come in two flavors: "same invention" and "obviousness-type." Both find their roots in the Patent Act,

specifically, § 101's allowance of "a" patent for new and useful inventions. *AbbVie*, 764 F.3d at 1372.

The Federal Circuit has prescribed a two-step obviousness-type double patenting analysis. The court first "construes the claim in the earlier patent [(sometimes referred to as the reference claim)] and the claim in the later patent and[] determines the differences." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001). The court next "determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Id.*; *see also AbbVie*, 764 F.3d at 1374, 1378 ("[T]he law of obviousness-type double patenting looks to the law of obviousness generally."). While obviousness of the asserted claim as compared to the reference claim is assessed considering the prior art, *In re Longi*, 759 F.2d 887, 893 (Fed. Cir. 1985), the written description of the earlier patent "cannot be used as though it were prior art," *Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1281 (Fed. Cir. 1992).

Double patenting is a question of law. *In re Basell Poliolefine Italia S.P.A.*, 547 F.3d 1371, 1375 (Fed. Cir. 2008). A challenger must prove invalidity based on obviousness-type double patenting by clear and convincing evidence. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1289–90 (Fed. Cir. 2012).

C. Anticipation

An asserted patent claim is invalid under § 102 of the Patent Act as anticipated if the accused infringer presents clear and convincing evidence that a single prior art reference discloses, either expressly or inherently, each limitation of the claim. *Brassica Protection Prods. LLC v. Sunrise Farms (In re Cruciferous Sprout Litig.)*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation . . . ." *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (quotation marks and citation omitted) (emphasis in the original).

D. Adequate Written Description and Enablement

Section 112 of the Patent Act requires that the specification of a patent "contain a written description of [(1)] the invention, and of [(2)] the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same." 35 U.S.C. § 112 (2006). Courts refer to these two requirements respectively as adequate written description and enablement.

The "hallmark" of an adequate written description is "disclosure." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). A patent must "reasonably convey[] to those skilled in the art that the inventor had

possession of the claimed subject matter as of the filing date" to satisfy the written description requirement. *Id.* An applicant establishes it was in possession of the invention "by describing the invention[] with all its claimed limitations." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (emphasis omitted). This description can be made using "words, structures, figures, diagrams, formulas, etc." *Id.* A patentee can also "rely on information that is 'well-known in the art' to satisfy written description." *Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1285 (Fed. Cir. 2012) (citation omitted). A challenger to the patent must prove invalidity based on inadequate written description by clear and convincing evidence. *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1072 (Fed. Cir. 2005). Whether the written description requirement has been met is a question of fact. *Id.*

To satisfy § 112's enablement requirement, the written description must provide a description that enables an artisan of ordinary skill to practice the full scope of the claimed invention without undue experimentation. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). "That some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive." *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984).

A challenger must prove invalidity based on non-enablement by clear and

convincing evidence. *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). Enablement is a question of law based on underlying facts. *Wyeth & Cordis*, 720 F.3d at 1384.

III. THE #309 PATENT (THE COMPOUND PATENT)

Claim 10 of the #309 patent claims ibrutinib, the active ingredient of Imbruvica®. Alvogen argues that claim 10 is invalid because it was anticipated by the so-called Pan article,[3] which was published on December 12, 2006. The parties agree that the Pan article and its Supporting Information (hereinafter collectively referred to as Pan) describe ibrutinib. They dispute, however, whether Pan was published before the date of ibrutinib's invention.

The date of a patented invention is "presumed to be the filing date of the application for the patent unless an earlier invention date is proved." *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449 (Fed. Cir. 1986). The application for the #309 patent was filed on December 28, 2006—16 days after Pan was published. Pharmacyclics argues, however, that under § 120 of the Patent Act the date of ibrutinib's invention is the filing date of either of two provisional patent applications the #309 patent inventors filed with the Patent &

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[3] Pan et al., *Discovery of Selective Irreversible Inhibitors for Bruton's Tyrosine Kinase*, 2 ChemMedChem 58–61 (2006) (DTX-541).

Trademark Office (PTO) before Pan was published—Provisional Application Nos. 60/826,720 (the #720 application), JTX-75, filed on September 22, 2006, and 60/828,590 (the #590 application), JTX-76, filed on October 6, 2006.

Section 120 provides that a patent application "for an invention disclosed in the manner provided by the first paragraph of section 112 of th[e] [Patent Act] in an application previously filed in the United States . . . shall have the same effect, as to such invention, as though filed on the date of the prior application." 35 U.S.C. § 120 (2006). The first paragraph of § 112 requires, among other things, that the patent have adequate written description and enable an artisan of ordinary skill to practice the invention. Alvogen argues that the provisional applications fail to satisfy both those requirements, and that, therefore, Pharmacyclics is not entitled to benefit under §120 from the earlier filing dates of the #720 and #590 applications.[4] Thus, the issue of whether Pan anticipates claim 10 turns on whether

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[4] Alvogen also argued for the first time in its posttrial briefing that the #309 patent is not entitled to benefit from the provisional applications' filing dates because Pharmacyclics failed to introduce evidence at trial that the provisional applications disclosed the best mode of practicing the invention. D.I. 325 at 9. Alvogen made no mention of best mode in the pretrial order or during trial and therefore waived any right to challenge the effective filing date of the #309 patent based on a failure to disclose best mode in the provisional applications. Alvogen argues in its reply brief, *see* D.I. 335 at 1 n.4, that the following statement in the pretrial order put Pharmacyclics on notice that it had to establish at trial that the provisional applications satisfied § 112's best mode requirement: "For the claim to be afforded the benefit of the priority date of an earlier-filed application, the earlier filed application must have a disclosure that provides support with respect to that claim

the provisional applications satisfy the written description and enablement requirements of § 112.

As the challenger of claim 10's validity, Alvogen bears the ultimate burden of proving by clear and convincing evidence that Pan anticipates the claim. *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1327 (Fed. Cir. 2008). But the Federal Circuit also held in *Videotek* that "once a challenger (the alleged infringer) has introduced sufficient evidence to put at issue whether there is . . . prior [anticipating] art that is dated earlier than the apparent effective date of the asserted patent claim, the patentee has the burden of going forward with evidence and argument to the contrary." *Id.* at 1329. The court stated that it "underst[ood] . . . the phrase 'going forward with evidence' to mean both producing additional evidence and presenting persuasive argument based on new evidence or evidence

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as required by 35 U.S.C. § 112." D.I. 283, Ex. 5A, ¶ 63. But the two sentences that immediately follow this sentence state: "Specifically, the parent application must have an adequate written description that conveys to [an artisan of ordinary skill] that the applicants were 'in possession' of the invention as ultimately claimed, at the time of filing the earlier-filed application. The parent [i.e., earlier filed] application must also enable [an artisan of ordinary skill] to make and use the invention without undue experimentation as of the filing date of the earlier application." D.I. 283, Ex. 5A, ¶ 63. (citations omitted). Thus, far from establishing that Pharmacyclics had the burden of producing best mode evidence at trial, the pretrial order instead made clear that Alvogen's specific arguments about the provisional applications made it necessary for Pharmacyclics to address at trial only whether those applications satisfied § 112's enablement and written description requirements.

already of record, as the case may require." *Id.* at 1327. And it held that the burden of going forward with evidence

> requires [the patentee] to show not only the existence of the earlier application, but why the written description in the earlier application supports the claim. In the context of the allegedly anticipating . . . prior art, that means producing sufficient evidence and argument to show that an ancestor to the [challenged] patent, with a filing date prior to the [prior art's publication] date, contains a written description that supports all the limitations of . . . the claim being asserted.

Id.

The court did not define "sufficient evidence and argument" or set forth standards to determine whether a patentee has shown that an ancestor to the patent's application contains adequate written description "as the case may require." The Federal Circuit has variously described the patentee's burden as (1) "provid[ing] a clear, unbroken chain of priority," *Droplets, Inc. v. E*TRADE Bank*, 887 F.3d 1309, 1317 (Fed. Cir. 2018), (2) "*prov[ing]* entitlement [to an earlier effective filing date] to . . . a federal court," *Nat. Alts. Int'l, Inc. v. Iancu*, 904 F.3d 1375, 1380 (Fed. Cir. 2018) (emphasis in the original), and (3) "establishing that its claimed invention is entitled to an earlier priority date," *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1376 (Fed. Cir. 2016). Wright & Miller, which *Videotek* cited in its discussion of the "burden of going forward with evidence" defines the standard for the burden of producing evidence as "sufficient evidence to support a

jury finding in [the plaintiff's] behalf." 21B Charles Alan Wright & Kenneth W. Graham, Jr., *Federal Practice & Procedure* § 5122 (2d ed. 2021).

A. Findings of Fact

1. Artisan of Ordinary Skill

An artisan of ordinary skill would have had a Ph.D. in chemistry, organic chemistry, or a related field. Pharmacyclics's expert—Dr. Paul Reider—used a slightly different definition of an artisan of ordinary skill but testified that his opinions related to the #309 patent would not change if he had used the above definition. Tr. 1472:24–1473:8.

2. Claim 10

Claim 10 of the #309 patent recites: "The compound of claim 1 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 at claim 10. The formula recited in claim 10 describes ibrutinib. Tr. 373:10–20, 1472:1–6. Claim 10 does not cover pharmaceutically acceptable salts of ibrutinib. Tr. 2064:4–23, 2066:24–2067:5, 2067:17–2068:16.

The #309 patent issued from U.S. Application No. 11,617,645 (the #645 application). The #645 application was filed on December 28, 2006 and claims priority to U.S. Provisional Application Nos. 60/826,720 (the #720 application), JTX-75, filed on September 22, 2006, and 60/828,590 (the #590 application), JTX-76, filed on October 6, 2006.

3. The Provisional Applications

a. Structure and Properties of Ibrutinib

Both the #720 application and #590 application disclose the structure of ibrutinib and refer to it as Compound 13. JTX-75 at 22 (Table 1, Compound 13); JTX-76 at 75 (Table 1, Compound 13); Tr. 1475:23–1476:9. An artisan of ordinary skill would have understood at the time each application was filed that each application disclosed the structure of ibrutinib. An artisan of ordinary skill would also have understood from the provisional applications' disclosure of ibrutinib's structure that the inventors possessed ibrutinib as of the date each application was filed.

The provisional applications also describe biological data obtained from experiments using ibrutinib that demonstrate ibrutinib's inhibition of BTK. Tr. 1475:23–1476:9; JTX-75 ¶¶ 71–78; JTX76 ¶¶ 282–292. An artisan of ordinary skill would have understood that the inventors could not have obtained the biological data unless they possessed ibrutinib. Thus, an artisan of ordinary skill would have understood that the inventors possessed ibrutinib before the filing dates of the applications.

b. Synthesis of Ibrutinib

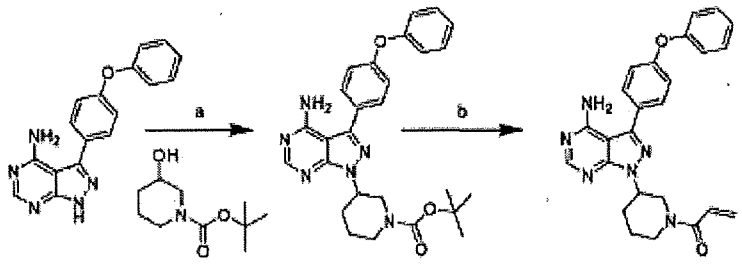
The provisional applications disclose a mixture of ibrutinib and ibrutinib's chiral counterpart. They refer to this mixture as Compound 4. "Chiral" molecules are asymmetric molecules that are mirror images of each other, i.e., they are related

like right and left hands. It is undisputed that an artisan of ordinary skill would have been able to isolate ibrutinib from its chiral counterpart using known methods. Tr. 412:10–413:2 (Alvogen's witness—Dr. Salvatore Lepore—testifying that it would have been "well-known in the art" how to separate the two molecules in Compound 4); Tr. 1477:24–1478:17 (Dr. Reider testifying that it would have been "quite straightforward" to separate the two molecules of Compound 4); Tr. 1574:14–1575:9 (Dr. Reider testifying that "you can just separate" the two molecules). Thus, it is undisputed that if an artisan could make Compound 4, she could make ibrutinib.

The parties dispute, however, whether the provisional applications enabled the synthesis of Compound 4. Stated more precisely, the parties dispute whether the provisional applications enabled the synthesis of a starting material (i.e., a reactant) that is referred to as "intermediate 2" or "known intermediate 2" (hereinafter referred to as "Intermediate 2") in the chemical reaction scheme disclosed in the provisional applications for Compound 4.

The two provisional applications both disclose the following reaction scheme for the synthesis of Compound 4:

Example 1: Synthesis of Irreversible Inhibitors



Scheme 1. Synthesis of irreversible Btk inhibitor 4 a) polymer-bound TPP, DIAD, THF; b) HCl/dioxane; then acryloyl chloride, TEA

JTX-75 at 25; JTX-76 at 77; Tr. 1477:24–1478:17. Scheme 1 and its accompanying text (hereinafter referred to collectively as the Compound 4 Scheme) are identical in both provisional applications except that the #590 application contains headings. The chemical structure above the "2" in the diagram of the reaction pictured above is Intermediate 2.

The provisional applications have a bracketed citation to the World Intellectual Property Organization patent WO 2001019829 (WO #829) immediately after they mention Intermediate 2. JTX-75 ¶ 80 ("To 101 mg of a known intermediate 2 [WO 2001019829] and 330 mg polymer-bound Triphenylphosphine (polymerlab) in 5 ml THF, 200 mg (2.0 eq.) of 3-OH N-Boc piperidine was added followed by 0.099 ml diisopropyl diazodicarboxylate."); JTX-76 ¶ 295 (same). An artisan of ordinary skill would have understood that the inventors cited WO #829 to explain how to synthesize Intermediate 2. Tr. 483:22–484:1, 1572:1–10, 1570:6–15, 1577:15–22. It is undisputed that this citation

would have enabled an artisan of ordinary skill to obtain WO #829 and to follow WO #829's instructions to synthesize Intermediate 2. Tr. 484:5–10 (Alvogen's expert, Dr. Lepore, agreeing that an artisan could follow WO #829 to synthesize Intermediate 2); Tr. 387:6–10, 478:19–479:10, 1479:8–1480:18 (Pharmacyclics's expert, Dr. Reider, testifying that an artisan could follow WO #829 to synthesize Intermediate 2).

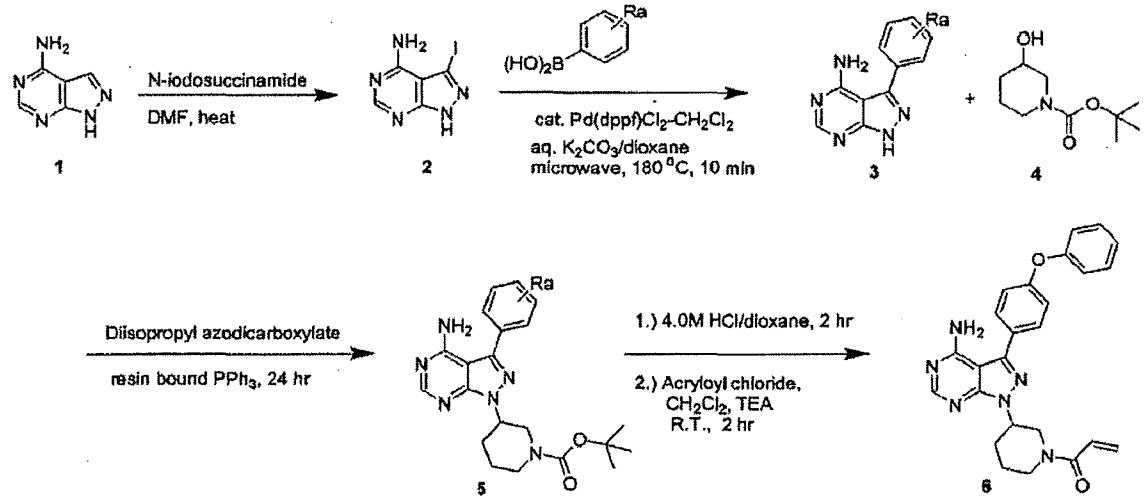
Using known techniques, an artisan of ordinary skill could also have synthesized Intermediate 2 without the teachings of WO #829 based on the structure of Intermediate 2 disclosed in the diagram of the Compound 4 Scheme. Dr. Reider testified that his undergraduate students—whose abilities would fall below that of a person with a Ph.D. in organic chemistry or related field (i.e., an artisan of ordinary skill)—would have been able to synthesize Intermediate 2 (or ibrutinib, for that matter) by working backwards from its structure to known starting compounds—a skill Dr. Reider referred to as retrosynthetic analysis. Tr. 1479:2–7, 1576:9–1577:1. Dr. Reider explained that it's a chemist's "job" to "synthesize molecules and build molecules," and that an artisan of ordinary skill would be expected to have "experience with the tool box of organic reactions and would understand how to form key bond connections." Tr. 1477:2–21. According to Dr. Reider, an artisan of ordinary skill would know, for example, how to join

different moieties in the molecule using well-known techniques such as a Mitsunobu reaction. *Id.*; *see also* Tr. 1481:1–20.

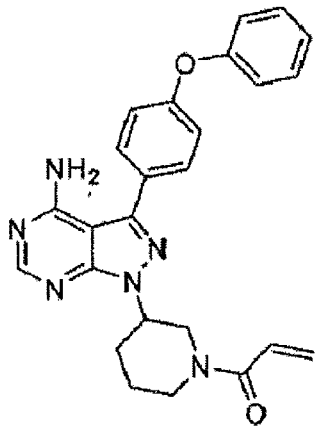
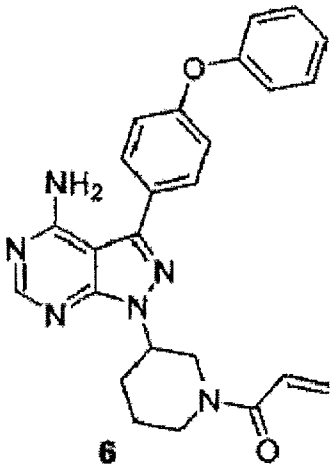
I find this testimony of Dr. Reider—and indeed Dr. Reider generally—to be credible. *See* Tr. 2056:21–2057:4. Based on that testimony, I find that the disclosure of the structure of Intermediate 2 in the Compound 4 Scheme would have enabled a skilled artisan to synthesize Intermediate 2. And, since it is undisputed that once a skilled artisan could synthesize Intermediate 2, she could synthesize Compound 4 and then separate ibrutinib from Compound 4, it follows that a skilled artisan could have synthesized ibrutinib with standard techniques based on the provisional applications' disclosure of the Compound 4 Scheme. Tr. 1477:24–1478:10.

The #590 application also discloses the following reaction scheme for the synthesis of so-called Compound 6.

Scheme I.



JTX-76 ¶ 110. Compound 6 is the same mixture of compounds as Compound 4:

Compound 4 (D.I. 76 at 77)	Compound 6 (D.I. 76 ¶ 110)
 4	 6

See also D.I. 336 ¶ 34. The synthesis described in Compound 6's Scheme I and its accompanying text (hereinafter referred to collectively as the Compound 6 Scheme) begins with a molecule the #590 application refers to as "Compound 1" and describes as being "commercially available." JTX-76 ¶ 110. The Compound 6 Scheme then describes the specific type of reaction and reagents necessary for each step of the synthesis of Compound 6 from Compound 1. *Id.* The Compound 6 Scheme also gives many of the reaction conditions (like temperature and solvent) for the various reaction steps. *See id.* And while it is true that the Compound 6 Scheme is missing some of the reaction details, *see* Tr. 396:13–397:18, 397:22–399:3 (Dr. Lepore testifying that the Mitsunobu reaction that synthesizes Compound 5 from Compounds 3 and 4 does not give the solvent or resin, the

relative amounts of Compounds 3 and 4, or the temperature conditions), it was within an ordinary artisan's skill to determine the missing reaction details because of the artisan's familiarity with the reaction types used in the Compound 6 Scheme, Tr. 1477:2–21 (Dr. Reider describing an artisan of ordinary skill's "experience with the tool box of organic reactions"); Tr. 1481:1–21 (Dr. Reider testifying that Mitsunobu reactions are normally run with one of two or three common solvents). Thus, an artisan of ordinary skill would have been able to synthesize Compound 6 using the teachings of the Compound 6 Scheme found in #590 application. *See* Tr. 1480:18–25. And, after using known techniques to separate the two molecules in Compound 6, an artisan of ordinary skill would be left with ibrutinib.

4. Pan (DTX-541 and DTX-542)

Pan discloses verbatim the Compound 4 Scheme set forth in the #720 and #590 applications. Tr. 481:8–482:1, 483:1– 484:10; *see* DTX-541 at -1457; DTX-542 at 2. Both Alvogen and Pharmacyclics agree that Pan enables and describes claim 10 of the #309 patent. *See* D.I. 335 at 1 n.3; Tr. 1491:16–20. Pan does not contain any disclosures related to the synthesis of Intermediate 2 or ibrutinib not described in the Compound 4 Scheme. Tr. 481:8–482:1, 483:1–484:10; *compare* JTX-75 at 25 *and* JTX-76 at 77 *with* DTX-541 at 2 *and* DTX-542 at 2.

B. Conclusions of Law

1. Written Description

Alvogen argues that the #720 and #590 applications lack adequate written description because they "fail to describe components essential for the synthesis of ibrutinib, and therefore [an artisan of ordinary skill] could not immediately discern that the applicants were in possession of ibrutinib." D.I. 325 at 9–10. But to satisfy the written description requirement of §112, a patent need not "describe components essential" to manufacture the invention. Words are not the only means to describe an invention. Structures, figures, and diagrams are also acceptable descriptive means to fully set forth the invention. *Lockwood* 107 F.3d at 1572. Here, the provisional applications' disclosure of ibrutinib's structure in Table 1 demonstrates that the inventors possessed the invention. *Ariad*, 598 F.3d at 1350 ("[A]n adequate written description requires a precise definition, such as by structure, formula, [or] chemical name . . . ."). Additionally, the inventors disclosed in the applications biological data that would not have been available to them had they not had ibrutinib to study. The disclosure of this biological data thus also demonstrates that the inventors possessed ibrutinib. Alvogen has therefore failed to show by clear and convincing evidence that the #720 and #590 applications do not adequately describe claim 10 of the #309 patent.

2. Enablement

Alvogen argues that Pharmacyclics "adduced no evidence (or argument) that[] a [skilled artisan] could synthesize ibrutinib based on the Applications without under experimentation." D.I. 335 at 1 (emphasis in the original). But I conclude as a matter of law that Pharmacyclics adduced sufficient evidence to satisfy its burden of going forward with evidence that the provisional applications would have enabled a skilled artisan to synthesize ibrutinib and further that Alvogen failed to establish by clear and convincing evidence that the applications would not have enabled a skilled artisan to synthesize ibrutinib without undue experimentation.

a. The Compound 4 Scheme with the Teachings of WO #829

The Compound 4 Scheme in the applications' written description would have enabled a skilled artisan to synthesize Compound 4 from Intermediate 2 and then to separate ibrutinib from its chiral counterpart in the mixture. The applications' citation to WO #829 would have enabled an artisan to synthesize Intermediate 2.

Alvogen argues in its briefing that the Compound 4 Scheme would not have enabled an artisan to synthesize ibrutinib from Intermediate 2. *See, e.g.*, D.I. 325 at 11. Alvogen never made this argument before or during trial and has therefore waived it. But in any event the argument is easily dismissed, as Alvogen admits

that Pan is enabling and it is undisputed that Pan does not contain any disclosures related to the synthesis of Intermediate 2 or ibrutinib not described in the Compound 4 Scheme.

Alvogen also argues that the provisional applications do not enable an artisan to synthesize Intermediate 2 because the Compound 4 Scheme "failed as a matter of law to incorporate [the teachings of WO #829] by reference." D.I. 325 at 11. This argument fails for two reasons.

First, the teachings of WO #829 were incorporated by reference in the Compound 4 Scheme set forth in the provisional applications. To incorporate material by reference, the host document

> must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. . . . In making that determination, the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity.

Zenon Environmental Inc. v. United States Filter Corporation., 506 F.3d 1370, 1378–79 (Fed. Cir. 2007) (quotation marks and citations omitted). Alvogen argues that the reference to WO #829 does not have the required particularity because the applicants "merely cited WO [#]829 in brackets without identifying (with any particularity) what subject matter the applicant sought to incorporate." D.I. 325 at

13.[5] But, this argument is foreclosed by Alvogen's admission that Pan is enabling even though Pan also discloses WO #829 "merely" in brackets and Pan says nothing about WO #829 that is not said in the provisional applications. Furthermore, as I found above, an artisan of ordinary skill would have understood that the inventors cited WO #829 to explain how to synthesize Intermediate 2 and it is undisputed that this citation would have enabled an artisan of ordinary skill to obtain WO #829. Thus, I conclude as a matter of law that the provisional applications incorporated by reference the relevant teachings of WO #829.

Second, Federal Circuit law is clear that no incorporation by reference is necessary in situations where the material was already known in the art. *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1365 (Fed. Cir. 2006).[6] In *Falkner*, the Federal Circuit held that an application's claim was enabled despite the

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[5] Alvogen faults the applicants for "fai[ing] to even use the terms 'incorporate' or 'reference.'" D.I. 325 at 13. It cites, however, and I know of, no statute, regulation, or caselaw that requires the use of the magic words "incorporate by reference" in order to incorporate a reference into a provisional application.

[6] Although *Falkner* deals with the necessity of incorporation by reference in a nonprovisional application, I find its holding to be applicable here since nonprovisional applications are held to a higher standard than provisional ones. *See* Manual of Patent Examining Procedure§ 608.01(p)(I)(B) (noting that the policy concerns which limit incorporation by reference "do[] not apply where the sole purpose for which an applicant relies on an earlier U.S. or foreign application is to establish an earlier filing date").

application's failure to disclose "essential" material or incorporate by reference any of the prior art documents disclosing it. *Id.* at 1365–67. The *Falkner* court reasoned that because the essential material was already in the prior art, an artisan of ordinary skill "would clearly have possessed such knowledge." *Id.* at 1365. Thus, "[t]he absence of incorporation by reference [was] not problematic" since "a patent need not teach, and preferably omits, what is well known in the art." *Id.* Here, there can be no dispute that the synthesis of Intermediate 2 was not novel since it was described in WO #829. Incorporation by reference (even though effectuated) was therefore not required.

b. The Compound 4 Scheme without the Teachings of WO #829

Even though I have concluded that WO #829 was incorporated by reference in the provisional applications, I will address Alvogen's argument that the provisional applications are not enabling because a skilled artisan could not synthesize Intermediate 2 without the benefit of WO #829 and undue experimentation.

I have already found, based on Dr. Reider's credible testimony, that a skilled artisan could have synthesized Intermediate 2 and thus ibrutinib without the benefit of WO #829 because the Compound 4 Scheme disclosed the structure of Intermediate 2. Alvogen cites *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361 (Fed. Cir. 1997) for the proposition that Dr. Reider's testimony is "insufficient" for

a finding of enablement. D.I. 335 at 1. But the court in *Genentech* held only that the knowledge of a skilled artisan cannot "supply the *novel* aspects of an invention in order to constitute adequate enablement." *Genentech*, 108 F.3d at 1366 (emphasis added). Indeed, "[a] patent need not teach, and preferably omits, what is well known in the art." *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987).

Here, there is no real dispute that the Compound Scheme 4 enabled the novel aspects of the invention. Alvogen's naked assertion in its reply brief that "the [provisional a]pplications do not disclose 'the novel aspects' of the purported invention," D.I. 335 at 3 n.6., is unsupported by any evidence (let alone clear and convincing evidence) and is refuted by Alvogen's admission that Pan is enabling. And, again, there is no dispute that the synthesis of Intermediate 2 was not novel since it was described in WO #829. The Compound 4 Scheme discloses a specific starting material (Intermediate 2) and the conditions under which the synthesis of Compound 4 can be carried out (the novel aspect of the invention). It thus enables the synthesis of ibrutinib without undue experimentation.

c. The Compound 6 Scheme

Pharmacyclics argues that the Compound 6 Scheme describes an additional method of synthesizing ibrutinib. The Compound 6 Scheme appears only in the #590 application. I have already concluded as a matter of law that the Compound

4 Scheme, which is found in both the #720 and #590 applications, is enabling. Because of that conclusion (and the fact that the parties gave what can charitably be called cursory attention to the Compound 6 Scheme in their briefing), I need not and do not address whether the Compound 6 Scheme is also enabling.

3. Conclusion

Pharmacyclics has produced sufficient evidence and argument to show that the #720 application and #590 application contain written descriptions that support all the limitations of claim 10 of the #309 patent. Alvogen, on the other hand, has failed to prove by clear and convincing evidence that claim 10 of the #309 patent is not entitled to the filing date of either the #720 application or #590 application. I therefore find that claim 10 of the #309 patent has a filing date of September 22, 2006. Claim 10 is presumed to have been invented on that date and therefore cannot be anticipated by Pan, since Pan's publication date is December 12, 2006. Claim 10 of the #309 patent is thus not invalid under § 102(a).

IV. THE #090 PATENT (THE METHOD OF TREATMENT PATENT)

Claim 2 of the #090 patent claims a method of treating relapsed or refractory mantle cell lymphoma (MCL) with a once-daily oral dose of about 560 mg of ibrutinib. Alvogen contends that claim 2 is invalid because it is not adequately described or enabled, is obvious in light of four prior art references, and constitutes obviousness-type double patenting.

A. Findings of Fact

1. Artisan of Ordinary Skill

An artisan of ordinary skill would have had a Ph.D. in chemistry, organic chemistry, or related field and/or an M.D.; several years of experience in treating cancer; and knowledge of and experience with various cancer therapies and oncology clinical trials. Pharmacyclics's expert—Dr. Simon Rule—used a slightly different definition of an artisan of ordinary skill but testified that his opinions related to the #090 patent would not change if he had used the definition stated above. D.I. 332 at ¶ 71.

2. Priority Date

The parties agree that the priority date for claim 2 is no earlier than June 3, 2010. Tr. 1248:25–1249:7, 1396:12–15.

3. Claim 2

Claim 1 of the #090 patent recites:

> 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 [of ibrutinib].

#090 patent at claim 1. Claim 2 depends from claim 1 and recites: "The method of claim 1, wherein the once per day oral dose is about 560 mg." #090 patent at claim 2.

4. R/R MCL and its Treatment

MCL is a rare and aggressive form of non-Hodgkin's lymphoma and is ultimately incurable. Tr. 1360:16–1361:20, 1321:11–18; PTX-226 at 2. MCL that has already been treated is referred to as relapsed and refractory mantle cell lymphoma (R/R MCL). Chemotherapy is typically used as the first treatment for MCL. R/R MCL is typically treated using a chemotherapy different from the chemotherapy first used to treat the patient's MCL. Tr. 1363:12–1364:2, 1367:9–22, 1363:17–24; PTX-226 at 2. As of June 2010, survival rates were low for MCL (4–5 years after diagnosis) and worse for R/R MCL (1–2 years). Tr. 1362:21–1363:3, 1366:1–1367:4 (citing JTX-620 at 8 (Fig. 5)); JTX-92 at 2 (outcomes "dismal in the relapsed setting" prior to June 2010).

Ibrutinib treats R/R MCL by binding to a protein called BTK and thereby disrupting the biological pathway through which R/R MCL proliferates. Because ibrutinib targets BTK, it is referred to as a BTK inhibitor. Tr. 355:10–18. And because ibrutinib will not unbind from BTK after it is joined to it, it is also said to be an irreversible BTK inhibitor. Tr. 360:1–5. The chemical moiety that binds ibrutinib to BTK belongs to a class of moieties known as Michael acceptors (so named because they undergo a Michael reaction). Tr. 1467:17–19, 1538:18, 1537:17–21.

An artisan of ordinary skill would not have considered irreversible BTK inhibitors or molecules with a Michael acceptor to be promising drug classes in June 2010. Tr. 1470:16–1471:7, 1371:2–6. Dr. Reider offered credible testimony at trial that the art in existence as of June 2010 taught away from using compounds with a reactive Michael acceptor group as drugs. Tr. 1471:2–12, 1532:14–1537:9, 1504:24–1505:20. Compounds with Michael acceptors were known at the time to be genotoxic (that is, they react with DNA and cause mutations) and carcinogenic, and to cause liver toxicity by depleting the body's stores of glutathione. Tr. 1532:14–1537:9 (referencing PTX-661 at 10 ("Michael acceptors are dangerous"); JTX-406 at 1, 6 ("Michael-type reaction has activity relevant to producing a genotoxic effect."); JTX-402 at 2, 6, 37 (disclosing in Table 1 that acrylamide—the Michael acceptor found in ibrutinib—produced carcinogenic effects in the adrenal tissue, central nervous system tissue, mammary gland tissue, oral cavity tissue, peritoneal cavity tissue, and pituitary gland tissue of rats). There was also a concern at the time that treating patients with an irreversible BTK inhibitor could cause the type of life-threatening infections experienced by patients affected by Bruton's disease (also known as X-linked agammaglobulinemia)—a disease caused by the body's inability to create BTK. Tr. 1507:22–1508:14, 1552:12–17, 1371:7–21, 1419:2–15; JTX-418 at 1.

5. Determining Ibrutinib's Therapeutic Dose

An artisan of ordinary skill would not have known or arrived at a dose of "about 560 mg" of ibrutinib for the treatment of R/R MCL as of the priority date. In 2009, the "3+3 method" was the prevailing procedure used to determine the therapeutic dose for a drug in a Phase I clinical trial. Tr. 1389:11–19; JTX-462 at 2–3. Under this method, clinicians administer a drug at increasing doses over time to one or two cohorts of three patients until the administered dose amount results in two patients in the same cohort experiencing unacceptable side effects. The dose-level immediately below that amount is deemed the maximum tolerated dose or "MTD," which usually becomes the dose used in a Phase II trial. JTX-462 at 3; Tr. 1389:20–1392:17, 1329:6–1331:4.

Pharmacyclics did not determine the claimed 560 mg dose using the traditional 3+3 method for its dose-escalation study. Tr. 1392:18–21. Instead of relying on ibrutinib's toxicity to determine dosage, Pharmacyclics looked at pharmacodynamics to determine the fraction of BTK bound to ibrutinib at a given ibrutinib dose. Tr. 1614:2–1615:3, 1393:20–1395:2, 1400:14–20; JTX-77 at 30, 36; JTX-461 at 2; *see also* Tr. 1606:2–20, 1608:16–1610:23. In other words, Pharmacyclics determined the point at which taking more ibrutinib could not cause a stronger therapeutic effect, instead of determining the point at which more ibrutinib would cause a patient harm (i.e., the MTD). A dose escalation study

using pharmacodynamics as its criterion (or endpoint) was abnormal at the time and represented "one of the most challenging aspects" of clinical trial design. Tr. 1400:21–1401:20; JTX-462 at 9; JTX-462 ("The [pharmacologically guided dose escalation] method has not been widely adopted due to practical obstacles[.]"). Alvogen's expert, Dr. Michael Grossbard, testified that he has "conducted dozens and dozens of clinical trials throughout [his] career" and has never used such a study design. Tr. 1238:23–1239:7, 1333:6–12. A dose escalation study that uses pharmacodynamic endpoints, therefore, cannot be classified as routine experimentation.

A dose of about 560 mg per day is not the MTD of ibrutinib. Tr. 1414:5–23, 1331:20–22. To this day, the MTD of ibrutinib is unknown and evidence shows it is greater than 840 mg. Tr. 1392:22–1393:11, 1414:21–23, 1331:17–19, 1348:23–25; JTX-461 at 2 ("MTD was not reached in [the Phase I study]"). Had an artisan of ordinary skill conducted a routine dose escalation study for ibrutinib before the priority date, she would have escalated the dose amount to a dose far greater than 560 mg.

6. Difficulty in Predicting Cancer Therapy Efficacy

Cancer treatment can be unpredictable. Tr. 1307:9–17 ("You can have a drug that can work in some patients and not in others."); Tr. 1369:7–1370:15 ("[D]o any of [the potential cancer treatment approaches] necessarily lead to

results or effective therapy? You have no idea until you actually try it."). Because of the unpredictability associated with the treatment of cancer, less than 5% of oncology drugs that enter a Phase I trial ultimately receive FDA approval. Tr. 1387:22–1388:1, 1307:21–1308:5; JTX-471 at 7 (3.4% of applications for oncology indications ultimately receive approval).

7. The Written Description

The #090 patent's written description describes in the Summary of the Invention, as an embodiment of the claimed invention, a method of treating R/R MCL using ibrutinib orally administered at a dose of about 560 mg per day. #090 patent at 4:52–5:1, 5:8–11; *see also* Tr. 1298:4–1300:2 (Alvogen's expert Dr. Grossbard agreeing that the Summary of the Invention "disclosed a 560-milligram dose of ibrutinib for the treatment of relapsed [and] refractory mantle cell lymphoma"). In fact, ibrutinib is the only BTK inhibitor that the written description specifically identifies as a treatment for R/R MCL. Tr. 1297:20–1298:3, 1433:18–1434:6; #090 patent at 4:59–5:1, 29:49–58.

Because ibrutinib is the only BTK inhibitor identified by name in the Summary of the Invention and is the only BTK identified for the treatment of R/R MCL, an artisan of ordinary skill would have understood as of the priority date that ibrutinib was the inventor's preferred BTK inhibitor for treating R/R MCL. #090

patent at 4:50–53, 4:59–5:40, 29:49–58; Tr. 1432:12–1434:16, 1297:12–1300:2, 1300:15–1301:8.

Example 13 in the written description discloses a protocol for a Phase II clinical trial to assess the use of BTK inhibitors at a dose of 560 mg per day to treat R/R MCL. #090 patent at 141:58–142:27. The purpose of Example 13 is to "[e]valuate the efficacy of BTK inhibitor in relapsed refractory subjects with MCL . . . ." *Id.* Although Example 13 does not explicitly identify a specific BTK inhibitor to use, an artisan of ordinary skill—having read the written description in its entirety—would understand to use the inventor's preferred BTK inhibitor (i.e., ibrutinib) in the Phase II protocol described in Example 13. Tr. 1433:18–1434:6.

An artisan of ordinary skill would have been able to follow the protocol of Example 13 using ibrutinib to practice the method recited in claim 2. Tr. 1434:11–1435:2, 1455:13–1456:8.

8. Prior Art

a. U.S. Patent Application Publication No. 2008/0076921 (the #921 publication) (DTX-484) and U.S. Patent No. 8,952,015 (the #015 patent) (DTX-6)

The #921 publication and #015 patent share essentially the same written description and differ only in their claims. Tr. 1295:18–25, 1412:16–22. The #921 publication and #015 patent are titled "Inhibitors of Bruton's tyrosine kinase" and disclose ibrutinib alongside other BTK inhibitors and methods of treating various

diseases using those BTK inhibitors. #921 publication at 1; #015 patent at 1; Tr. 1277:18–22.

The #921 publication and #015 patent disclose ibrutinib by its chemical name (referred to in the patent as "Compound 13") and its structure and a method of synthesis in Example 1b. #921 publication ¶¶ 22, 450–451; #015 patent at 4:19–21, 96:40–97:4; Tr. 1278:5–13. The #921 publication and #015 patent also disclose at least ten other BTK inhibitors by name, *see* #921 publication ¶ 22 (naming compounds 4–6, 8–12, 14, and 15); #015 patent at 4:1–26 (same), and dozens more by structure, #921 publication ¶¶ 252–253; #015 patent at 36:30–51:37.

While the #921 publication and #015 patent discuss using the disclosed BTK inhibitors to treat MCL, #921 publication ¶¶ 170, 174; #015 patent at claims 17–20, 25:66–26:18, 26:60–27:2; Tr. 1278:14–25, they do not disclose the use of ibrutinib to treat R/R MCL, Tr. 1413:23–1414:4. They do, however, disclose that BTK inhibitors can be used to treat "a mind boggling number of [other] conditions . . . includ[ing] everything from pneumonia to heart attacks to non-malignant conditions to a whole host of malignant conditions, including some things [Dr. Rule had] never heard of." Tr. 1413:7–15; *see* #921 publication ¶¶ 33–51 (while I have not undertaken a meticulous counting of each condition listed, a

rough estimation using a word counting program suggests that approximately 400 conditions are disclosed in the cited portion); #015 patent at 5:47–9:49 (same).

The publication's and patent's disclosures also state that a therapeutically effective amount of a drug can be determined through a dose escalation study with "routine experimentation." #921 publication ¶ 140; #015 patent at 21:25–52; Tr. 1279:23–1280:6. The #921 publication and #015 patent provide a general dose range of 0.02–5000 mg per day or from about 1–1500 mg to day to treat the conditions listed in the written description. #921 publication ¶ 410; #015 patent at 84:23–38; Tr. 1413:17–1414:4, 1324:18–1325:2. Neither the #921 publication nor the #015 patent disclose any specific dose for any particular condition. Tr. 1413:23–1414:4.

b. Pollyea (DTX-467)

Pollyea is titled "A Phase I Dose Escalation Study of the Btk Inhibitor PCI-32765 in Relapsed and Refractory B Cell Non-Hodgkin Lymphoma and Use of a Novel Fluorescent Probe Pharmacodynamic Assay." DTX-467; Tr. 1281:18–25. PCI-32765 refers to ibrutinib. Tr. 1605:1–10, 1658:19–1659:1, 1701:12–24.

Pollyea published the interim results for seven patients in a Phase I dose escalation study of ibrutinib. Pollyea describes dosing based on subject weight—specifically, 1.25 mg of drug per kg of the patient's body weight (mg/kg/day); it does not disclose a fixed daily dose of about 560 mg per day. DTX-467 at -536;

Tr. 1404:22–1405:1. Although a Phase I study focuses on a drug's safety as opposed to efficacy, Pollyea reported that none of the seven patients were observed to show partial or complete responses to treatment. DTX-467 at -537. In oncology, a partial response is defined as a "decrease in the disease by 50 percent or more but not . . . a complete response." Tr. 1245:21–1246:3. A complete response or complete remission means the cancer essentially disappears. *Id.*

c. December 2009 Press Release (DTX-137)

This press release reports subsequent interim results of the same Phase I dose escalation study of PCI-32765 (i.e., ibrutinib) disclosed in Pollyea. Sixteen lymphoma patients were enrolled in the study. DTX-137 at 1. Among the patients with partial responses, two were R/R MCL patients and one was a R/R follicular lymphoma patient. DTX-137 at 1; Tr. 1410:3–10, 1406:24–1407:13.

9. Comparison of Claimed Limitations with the Prior Art

Claim 2 of the #090 patent claims the treatment of R/R MCL with a once-daily oral dose of about 560 mg of ibrutinib. Of Alvogen's four cited references, only Pollyea and the December 2009 Press Release disclose treating R/R MCL with ibrutinib. None of the references disclose treating R/R MCL with a once-daily dose of 560 mg. Pollyea and the December 2009 Press Release describe dosing based on subject weight—e.g., 1.25 mg of drug per kg of patient's body weight (mg/kg/day); neither reference mentions any fixed dose.

10. Obviousness

Alvogen argues that claim 2 is invalid for obviousness because an artisan of ordinary skill would have been motivated to combine the teachings of the #015 patent (and the #921 publication), Pollyea, and the December 2009 Press Release to achieve the invention recited in claim 2 and would have had a reasonable expectation of success in doing so.[7] The inventors of the #090 patent cited all four of these references to the PTO during the patent's prosecution. #090 patent at pages 3–9.

a. Motivation

Alvogen argues that an artisan of ordinary skill would have been motivated to use ibrutinib to treat R/R MCL because the Phase I dose escalation study disclosed in Pollyea and the December 2009 Press Release shows "that ibrutinib is efficacious in treating R/R MCL." D.I. 325 at 27. But given the unpredictable nature of oncology and the fact that only two of the study's patients had R/R MCL, an artisan of ordinary skill would not interpret these results as showing that ibrutinib could be used as a treatment for R/R MCL. Tr. 1407:2–10, 1410:3–15.

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[7] Alvogen lists Advani (DTX-136) as relevant prior art. *See* DI 325 at 23. Advani, however, is not among the combination of references that Alvogen argues renders claim 2 obvious. *See* DI 325 at 26 (heading titled "Obviousness in View of '015 Patent (or '921 Publication), Pollyea 2009 and the December 2009 Press Release"). I have considered Advani's teachings as background prior art in making my findings of fact and conclusions of law.

The mere fact that ibrutinib was being studied in a Phase I trial does not speak to ibrutinib's efficacy. Indeed, less than five percent of oncology drugs that enter a Phase I trial ultimately receive FDA approval. Tr. 1415:12–19. Thus, reading these references would not have motivated an artisan of ordinary skill to use ibrutinib to treat R/R MCL.

Additionally, none of Alvogen's references alone or in combination would have motivated an artisan of ordinary skill to use a once-daily dose of about 560 mg. As noted above, none of the references suggested the use of a once-daily dose to treat R/R MCL. The only references that mention R/R MCL[8]—Pollyea and the December Press Release—disclose a weight-based dosing regimen. Nor does the evidence suggest that a conventional 3+3 dose escalation study would lead to a

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[8] Alvogen's briefing implicitly asserts that a disclosure of treating MCL with ibrutinib is relevant to whether an artisan of ordinary skill would be motivated to treat R/R MCL with ibrutinib. *See* D.I. 325 at 27. Inherent in this implicit assertion is that therapies for MCL and R/R MCL are similar enough that an artisan of ordinary skill would interpret a disclosure of treating MCL with a drug as evidence that the drug would be effective at treating R/R MCL. But the evidence adduced at trial shows that although MCL and R/R MCL might be different stages of the same disease, they behave and were treated differently. For example, R/R MCL is considered more aggressive and has a worse rate of survival. R/R MCL is more difficult to treat, and a therapy used to treat MCL is typically not used to treat R/R MCL in the same patient. For these reasons, I find that Alvogen has not shown by clear and convincing evidence that an artisan of ordinary skill would interpret a disclosure of treating MCL with a drug as evidence that the drug would be effective at treating R/R MCL.

dose of about 560 mg. A typical 3+3 dose escalation study using toxicity as an endpoint would have reached the MTD as the dosage. Dr. Grossbard admitted that the MTD for ibrutinib is above 560 mg. To reach the claimed dose of about 560 mg, an artisan would need to conduct a study using pharmacodynamic endpoints, something that none of the references would have motivated an artisan of ordinary skill to do. In fact, Dr. Grossbard—who testified that he has "conducted dozens and dozens of clinical trials throughout [his] career"—has never conducted a dose escalation study using pharmacodynamic endpoints. Tr. 1238:23–1239:7, 1333:6–12.

Finally, safety concerns about ibrutinib would have discouraged an artisan of ordinary skill from treating R/R MCL with ibrutinib. Specifically, an artisan of ordinary skill would have been concerned that treating a patient with a BTK inhibitor could cause life-threatening infections similar to those experienced by patients suffering from Bruton's disease who are born without BTK. And an artisan of ordinary skill would have also had safety concerns about using an irreversible inhibitor with a reactive Michael acceptor because those acceptors were known to be genotoxic and carcinogenic and to cause liver toxicity.

Accordingly, I find that Alvogen has failed to demonstrate by clear and convincing evidence that an artisan of ordinary skill would be motivated to treat R/R MCL with a once-daily dose of about 560 mg of ibrutinib.

b. Reasonable Expectation of Success

Alvogen argues that "the prior art clinical trial results" (i.e., Pollyea and December 2009 Press Release) would have provided an artisan of ordinary skill with a reasonable expectation of success in treating R/R MCL with a 560 mg daily dose of ibrutinib. But again, the preliminary results from the ongoing Phase I trial reported in Pollyea and the December 2009 Press Release did not teach the efficacy of ibrutinib for treating R/R MCL, and an artisan of ordinary skill could not have reasonably expected success in light of the unpredictable nature of oncology and the study's extremely small sample size. To the contrary, as I found above, R/R MCL is an aggressive lymphoma that is even more difficult to treat than MCL. An artisan of ordinary skill would thus not have had a reasonable expectation of success in treating R/R MCL with ibrutinib in the absence of more conclusive evidence of its efficacy.

Alvogen also argues that the #015 patent and #921 publication teach that a dose escalation study could be used to arrive at the claimed daily oral dose of about 560 mg through "routine experimentation." D.I. 325 at 27. But the #015 patent and #921 publication's boilerplate references to "routine experimentation" do not suggest a dose escalation study using pharmacodynamic endpoints since such an experiment is not "routine." Thus, Alvogen's cited prior art does not suggest using a once-daily dose of about 560 mg.

Accordingly, I find that Alvogen has failed to show by clear and convincing evidence than an artisan of ordinary skill would have had a reasonable expectation of success in treating R/R MCL with a once-daily oral dose of about 560 mg of ibrutinib.

c. Secondary Considerations

1) Long-felt but Unmet Need

Before Imbruvica®, the available treatment options for R/R MCL—i.e., chemotherapy—had "dismal" outcomes and were "often associated with severe side effects." JTX-92 at 2; *see* PTX-226 at 2 ("More effective agents are needed."); Tr. 1358:3–9, 1360:4–10 (Dr. Rule testifying to a "long history" of failed agents); Tr. 1364:21–1367:22. Because of the shortcomings associated with the prior treatment options, there was a long-felt but unmet need for safer and more effective methods of treating R/R MCL. Using Imbruvica® to treat R/R MCL met those needs. Imbruvica®'s label and prescribing information indicate that it treats R/R MCL with a once-daily oral dose of 560 mg of ibrutinib. DTX-1413 at 2. Imbruvica® was more effective than the prior art at treating R/R MCL, a fact indicated by its higher overall response rate (ORR).[9] JTX-92 at 6 (showing the ORR for Imbruvica® (68%) and other approved treatments for R/R MCL, including

[9] An overall response rate is the combination of the rates of partial responses and the rates of complete responses. Tr. 1245:21–1246:3.

bortezomib (33%), lenalidomide (28%), and temsirolimus (22%)); *see also* PTX-226; Tr. 1376:3–1377:1, 1377:6–1378:5. Imbruvica® is safer than standard chemotherapy treatments because the claimed method is well-tolerated and has a low incidence of side effects. *Compare* Tr. 1381:14–1382:15 (side effects for treatment of R/R MCL with ibrutinib were most commonly mild bruising and temporary diarrhea) *with* Tr. 1420:7–10 ("Give people chemotherapy. You don't live a quality[] life. These patients are washed out for a long, long time. Remember that chemotherapy kills people as well. There's a mortality at two percent."). Imbruvica® thus met a long-felt need for a safer and more effective method of treating R/R MCL.

This long-felt need for a safer and more effective method of treating R/R MCL was particularly pressing for elderly patients. R/R MCL presents primarily in the elderly, who are generally less able to tolerate the side effects of chemotherapy. Tr. 1420:14–16 ("[T]he average age of presentation is 70, so by the time you relapse, you're mid seventies. . . . This drug just changes your approach to that condition."); Tr. 1364:15–20 ("[P]robably 10 to 15 percent of [R/R MCL] patients are too old or too frail to consider any of those [chemo]therapies"); Tr. 1367:9–22, 1374:20–1375:1 ("There is no chemotherapy you can give [a 92-year-old] that's going to be effective without causing very, very significant side effects and probably kill him."). Treating R/R MCL with Imbruvica® meets this need as

well. *See* Tr. 1381:14–1382:15 (the claimed treatment method is "incredibly well tolerated, and that's what's particularly useful in the context of elderly patient who often have significant effects of comorbidity. There are no contraindications. That's very important."); *see also* PTX-1343 at 1 (Imbruvica® label listing no contraindications); Tr. 1420:5–19. I find this evidence to be particularly compelling.

In short, there existed as of the priority date a long-felt but unmet need for a more effective and safer method of treating R/R MCL that was met by Imbruvica®.

2) Failure of Others

When developing cancer treatments, researchers often try to identify the molecules necessary for a cancer to persist or proliferate and then develop drugs to target those molecules. Tr. 1367:23–1368:9; Tr. 1420:24–1422:9. And at the time of the priority date, many pharmaceutical companies had tried and failed to develop a safer and more effective R/R MCL therapy by targeting molecules thought to play a role in the progression of R/R MCL. *Id.*; Tr. 1383:21–1384:5. Companies, for example, had tried and failed to develop drug candidates that would target and inhibit the proteins Bcl-2 and Pi3K. Tr. 1368:10–15, 1369:3–6 (Bcl-2 and Pi3K inhibitors thought to affect cell death). A company had tried but failed to develop drugs that would target and inhibit vascular endothelial growth factor (VEGF). Tr. 1368:16–20 (anti-VEGF agents believed to shrink tumors by

reducing blood supply). Another company attempted and failed to develop bespoke surface antibodies that would target pathways related to R/R MCL. Tr. 1368:21–1369:2. These failed attempts support a finding that others had failed to develop a more safe and effective method of treating R/R MCL.

3) Skepticism

As I explained above, concerns that inhibiting BTK in patients could cause life-threatening infections similar to those experienced by patients affected by Bruton's disease would have discouraged a skilled artisan from using a BTK inhibitor like ibrutinib as a drug as of the priority date. A skilled artisan also would have had safety concerns about using an irreversible inhibitor with a reactive Michael acceptor group because Michael acceptors were known to be genotoxic and carcinogenic and to cause liver toxicity. These concerns would have made a skilled artisan skeptical that ibrutinib could be safely administered to patients.

Real-world evidence of these concerns is demonstrated by the fact that numerous pharmaceutical companies rejected Pharmacyclics's initial efforts to jointly develop ibrutinib, because they had concerns about ibrutinib's safety. Tr. 1549:12–1552:1 (discussing communications from large pharmaceutical companies—including Amgen, Boehringer Ingelheim, and GlaxoSmithKline—expressing concern about irreversible BTK inhibition (referencing JTX-186; JTX-

192; JTX-191; JTX-188)). Skepticism about the use of ibrutinib to safely treat patients with R/R MCL thus supports a finding of nonobviousness.

4) Unexpected Results

Given the difficulty of treating R/R MCL, the long-felt need for safer and more effective methods of treating R/R MCL, the failure of others to develop such methods, and skepticism of safely treating patients with ibrutinib, an artisan of ordinary skill would not have expected that using Imbruvica® to treat R/R MCL would be more effective and safer than prior treatments.

5) Praise

The National Organization for Rare Disorders recognized Imbruvica® as a "innovative new therap[y]" for treating R/R MCL when it awarded Pharmacyclics a "Partners in Progress Award" specifically for Imbruvica®'s FDA approval in treating R/R MCL. JTX-107 at 3; Tr. 1423:6–17.

6) Commercial Success

Evidence adduced at trial demonstrates that Imbruvica® tablets and capsules are a commercial success. Tr. 1919 5–9, 1877:9–14, 1881:10–18. After FDA approval, Imbruvica® quickly achieved, and has since maintained, a large share of the market of R/R MCL patients. JTX-308; JTX-309; Tr. 1879:2–1880:20 (total patient share for R/R MCL is around 50%). Moreover, Alvogen does not contest in its opening brief that Imbruvica® tablets and capsules were commercially successful. *See* D.I. 325 at 32–33.

B. Conclusions of Law

1. Enablement

Alvogen has failed to establish by clear and convincing evidence that claim 2 is not enabled by the patent's written description. Example 13 provides a protocol to evaluate the efficacy of treating R/R MCL with a BTK inhibitor. The protocol instructs that the BTK inhibitor should be administered at a dose of 560 mg per day. Given the Summary of the Invention's focus on ibrutinib as the specific BTK inhibitor to be used in treating R/R MCL, an artisan of ordinary skill would understand from reading the patent that ibrutinib is to be used as the "BTK inhibitor" of Example 13. *Application of Johnson*, 558 F.2d 1008, 1017 (C.C.P.A. 1977) ("[T]he specification as a whole must be considered in determining whether the scope of enablement provided by the specification is commensurate with the scope of the claims."). And 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. That Example 13 is a "hypothetical clinical trial" with "no actual clinical results," D.I. 325 at 17–18, is immaterial since "efficacy data are generally not required in a patent application." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1310 (Fed. Cir. 2015) (citation omitted).

2. Written Description

Alvogen argues that claim 2 "lacks adequate written description because it overreaches the scope of the inventor's contribution to the field of art as described

in the patent specification, which merely discloses nothing more than a hoped-for function for an as-yet-to-be discovered invention." D.I. 325 at 16 (citations, alterations, and quotation marks omitted). I disagree. As I just explained, Example 13, when read in the light of the remainder of the written description, enables and describes claim 2 of the #090 patent. In addition, the written description also describes a method of treating R/R MCL using ibrutinib orally administered at a dose of about 560 mg/day, i.e., claim 2. #090 patent at 4:52–5:1, 5:8–11; Tr. 1298:4–1300:2. Alvogen has therefore failed to establish by clear and convincing evidence that claim 2 is not adequately described.

3. Obviousness

I have already found as a factual matter that Alvogen did not prove by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success the teachings of the prior art to achieve the claimed method of treating R/R MCL with a once-daily dose of about 560 mg of ibrutinib. These factual findings are fatal to Alvogen's obviousness theory.

Secondary considerations also counsel against a finding of obviousness. The evidence adduced at trial showed a long-felt but unmet need, failure of others, unexpected results, and skepticism. Of these secondary considerations, I find

especially probative the existence of a long-felt but unmet need for a treatment of R/R MCL that was better tolerated by the elderly.

Imbruvica®'s commercial success also supports a finding of nonobviousness. Alvogen argues that Pharmacyclics failed to demonstrate a nexus between the method of treatment claimed in claim 2 and Imbruvica®'s success. But "[a] prima facie case of nexus is made when the patentee shows both that there is commercial success, and that the product that is commercially successful is the invention disclosed and claimed in the patent." *Crocs, Inc. v. U.S. Int'l Trade Comm'n*, 598 F.3d 1294, 1310–11 (Fed. Cir. 2010). And Pharmacyclics has made a prima facie case here since Imbruvica®'s label indicates that "560 mg [is to be] taken orally once-daily" for the treatment of R/R MCL. PTX-1343 at 1.

"Once the patentee demonstrates a prima facie nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger." *Id.* Alvogen, however, has offered no evidence that Imbruvica®'s commercial success is caused by unclaimed features of the invention. Accordingly, Imbruvica®'s commercial success weighs in favor of a finding of nonobviousness. But I also note that even if, as Alvogen claims, there were no relevant evidence of commercial success, I would not change my ultimate conclusion with respect to the obviousness of claim 2 since the evidence of the secondary considerations "is not a requirement for patentability." *Custom Accessories, Inc. v. Jeffrey-Allan Ind., Inc.*, 807 F.2d 955,

960 (Fed. Cir. 1986); *see also id.* ("[T]he absence of objective evidence is a neutral factor.").

In short, I conclude as a matter of law that Alvogen failed to establish that claim 2 of the #090 patent is invalid as obvious under § 103.

4. Obviousness-Type Double Patenting

Alvogen argues that claim 2 of the #090 patent is invalid for obviousness-type double patenting because "the [#]015 [p]atent describes a 'therapeutically effective amount' as between 1 and 1500 mg ibrutinib, which includes the 'about 560 mg' ibrutinib" in claim 2 of the #090 patent. D.I. 325 at 25. As noted above, when addressing an obviousness-type double patenting challenge to a patent, the court first "construes the claim in the earlier patent and the claim in the later patent and determines the differences." *Eli Lilly*, 251 F.3d at 968. The court next "determines whether the differences in subject matter between the two claims render the claims patentably distinct." *Id.*

Claim 20 of the #015 patent and claim 2 of the #090 patent differ in numerous ways. Claim 20 claims a method of treating any of ten lymphomas—including MCL, but not R/R MCL—whereas claim 2 claims a method of treating R/R MCL. Claim 20 generally claims administration of "a therapeutically effective amount" of ibrutinib, whereas claim 2 recites a fixed dose of about 560 mg of ibrutinib per day. Claim 20 does not recite the spacing of the doses (e.g.,

every other day, once-daily, twice daily, etc.), whereas claim 2 requires a single dose administered each day. Claim 20 does not recite how the dose is to be administered, whereas claim 2 requires that the dose be orally administered.

Although claim 20 indisputably does not claim a numerical dosage amount or range, Alvogen contends that claim 20's "therapeutically effective amount" is not patentably distinct from claim 2's "about 560 mg" dosage amount. In support of this contention it argues (1) that because the #015 patent's written description discloses a dosage range of between 1 and 1500 mg ibrutinib, "there is a presumption of obviousness" that Pharmacyclics has not rebutted, D.I. 325 at 25–26 (citation omitted); and (2) that claim 2 of the #090 patent "is obvious because the 'therapeutically effective amount' could be determined (according to the [#]015 [p]atent) through 'routine experimentation,'" D.I. 325 at 26. These arguments conflate single-reference obviousness with obviousness-type double patenting and improperly use the #015 patent's written description as prior art in an obviousness-type double patenting analysis. Obviousness-type double patenting "is altogether a matter of what is claimed," and Federal Circuit "precedent makes clear that the *disclosure* of a patent cited in support of a double patenting rejection cannot be used as though it were prior art." *Gen. Foods Corp.*, 972 F.2d at 1281 (emphasis in the original).

Because Alvogen never raised the defense of single-reference obviousness in the Pretrial Order, it has waived these arguments. Were I to address the merits of Alvogen's arguments, I would reject them for at least four reasons. First, there is no presumption of obviousness attached to a dosage amount that falls within the 1–1500 mg range disclosed in the #015 patent's written description. A presumption of obviousness "attaches only when 'the range or value of a particular variable' is '*the* difference between the claimed invention and the prior art.'" *Tris Pharma, Inc. v. Actavis Labs. FL, Inc.*, 2020 WL 7028456, at *15 (D. Del. 2020) (emphasis in the original) (citing *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1577 n.3 (Fed. Cir. 1993)). As noted above, there are many differences between the claimed invention and claim 20, including the applicable disease, route of administration, and number of administrations per day.

Second, the #015 patent's written description actually discloses two ranges of doses from "0.02-5000 mg per day, or from about 1-1500 mg per day," administered in a single dose or many doses per day, #015 patent at 84:31–38, through several potential routes of administration, #015 patent at 62:13–17. The breadth of these ranges in the written description is another reason the presumption of obviousness does not apply. *Allergan*, 796 F.3d at 1305 (burden may not shift to patentee where ranges are so broad as to encompass a very large number of distinct possibilities).

Third, the presumption is a "specific application" of the general legal principle that "it is not inventive to discover the optimum or workable ranges by routine experimentation." *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018). But, as discussed above, routine experimentation would not have resulted in a dose amount of 560 mg.

Fourth, the evidence Pharmacyclics adduced at trial would have rebutted any presumption of obviousness. As discussed above, the disclosures in the #015 patent in combination with the additional disclosures of the #921 publication, Pollyea, and the December 2009 Press Release do not render claim 2 of the #090 patent invalid for obviousness.

It follows that the #015 patent by itself does not invalidate the #090 patent under a theory of single-reference obviousness. It also follows that differences in subject matter between claim 20 of the #015 patent and claim 2 of the #090 patent render the claims patentably distinct. *Amgen Inc. v. F. Hoffmann-La Roche, Ltd.*, 580 F.3d 1340, 1361 (Fed. Cir. 2009) (determining whether the differences in subject matter between the two claims render the claims patentably distinct "is analogous to an obviousness analysis under 35 U.S.C. § 103").

V. THE #455 PATENT (THE CRYSTALLINE FORM PATENT)

Claim 5 of the #455 patent is directed to a crystalline form of ibrutinib. Alvogen contends that claim 5 is invalid because (1) it is inherently anticipated by

Pollyea and Fowler; and (2) it is obvious in light of Honigberg, Miller, and U.S. Patent No. 7,514,444 (the #444 patent).

A. Findings of Fact

1. Artisan of Ordinary Skill

An artisan of ordinary skill would have had a bachelor's degree in chemical engineering, pharmaceutical science, or a related field, with some knowledge of solid state or analytical chemistry, and several years of experience in the pharmaceutical industry, which would include experience with analytical techniques used in the industry; or somebody with an advanced degree in one of these fields with less experience. Alvogen's expert—Dr. Jennifer Swift— used a slightly different definition of an artisan of ordinary skill but testified that her opinions related to the #455 patent would not change if she had used the definition stated above. Tr. 563:14–564:3.

2. Priority Date

The #455 patent has a priority date no later than June 4, 2012. JTX-9 at 2; Tr. 553:6–11; D.I. 276-1 Ex. 1, ¶ 57.

3. Crystalline Forms

Solids are either amorphous or crystalline in form. The constituent atoms or molecules of an amorphous solid are randomly arranged. The constituent atoms or molecules of a crystalline solid are arranged in definite and repeating patterns. Tr. 706:9–17, 531:2–12, 531:25–532:8. These repeating patterns, often referred to as

"packing arrangements," vary. When a compound has more than one crystalline form (because its constituent atoms or molecules can have more than one packing arrangement), it is said to exhibit polymorphism and the crystalline forms of such a compound are sometimes referred to as polymorphs. Tr. 706:18–25.

Polymorphs can exhibit markedly different physical properties. For example, graphite and diamonds are both polymorphs of carbon, but the two materials vary substantially in their hardness—a difference entirely attributable to their different crystalline forms. Tr. 531:2–24. The crystalline form of a pharmaceutical compound can affect the compound's stability, safety, and efficacy. Tr. 532:11–533:9. In general, a pharmaceutical formulator prefers to use a crystalline form that is highly stable in order to reduce the likelihood that the compound will convert to a physical form that might be less safe or efficacious. DTX-1008 at 18–20; Tr. 539:11–22. That said, a drug product may contain an active ingredient in an amorphous or metastable form. Tr. 632:21–633:1, 640:5–9, 641:1–3; *see also* DTX-1025 at -936.

Discovering new crystalline forms is challenging and unpredictable. DTX 2188 at -0197 ("Obtaining new crystal forms, whether by systematic search or by serendipity, is an adventure into the crystallographic unknown, and preparing or recognizing a new crystal form is undeniably a chemical invention."); Tr. 788:7–21, 1730:18–1731:13; DTX-1008 at 16 ("Which polymorph of a crystalline drug

will form under certain conditions cannot be predicted."). An experiment designed to discover new polymorphs is referred to as a polymorph screen.

4. X-Ray Powder Diffraction

X-ray powder diffraction (XRPD) is the most common method of distinguishing and identifying polymorphs. Tr. 533:10–22. XRPD works by bombarding a crystalline form sample with x-rays and measuring the intensity of x-rays that are scattered (i.e., diffracted) off the sample. XRPD experiments produce plots—called XRPD patterns—that are unique to the crystalline form being studied. These plots contain various peaks associated with the angle of diffraction (referred to as 2-Theta). DTX-1008 at 19; Tr. 533:23–534:21, 534:25–535:15.

5. Claim 5 and Crystalline Forms of Ibrutinib

Claim 5 depends from claim 1 and is directed to "[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°," and that "further comprises 2-Theta peaks at 13.6±0.1°, 16.1±0.1°, and 21.6±0.1°." #455 patent at claims 1, 5. Crystalline Form A is the most stable form of ibrutinib currently known.

The written description of the #455 patent teaches that ibrutinib exists in multiple crystalline forms and in an amorphous form. #455 patent at 10:17–50; *see also* Tr. 625:17–24, 640:5–9, 641:1–3, 1701:13–1702:3, 1657:25–1659:10.

6. Prior Art for Anticipation—Pollyea (DTX-467) and Fowler (DTX-148)

Pollyea discloses interim results of a dose escalation study conducted by Pharmacyclics of PCI-32765, an orally administered covalent inhibitor of BTK. DTX-467 at -536–37; Tr. 566:1–10. Fowler discloses updated results of the study. DTX-148 at -901–02; Tr. 594:2–595:6.

PCI-32765 refers to ibrutinib. DTX-278 at -682; Tr. 1605:1–10, 1658:19–1659:1, 1701:12–24. But PCI-32765 does not refer to a particular form (e.g., amorphous or crystalline) of ibrutinib. *Compare* JTX-334 at 1, 8 (describing PCI-32765 as having the "consistency of foam," making the sample amorphous, Tr. 1659:6–10) *with* JTX-551 at 9, tbl. 1 (listing two other crystalline forms of ibrutinib—Forms B and C—under the code name PCI-32765); *see also* Tr. 649:10–650:19 (Dr. Swift admitting that she was unsure what form of ibrutinib PCI-32765 referred to); Tr. 1697:15–1698:3, 1699:4–1702:3 (Dr. Myerson explaining that PCI-32765 does not refer to a particular form of ibrutinib); Tr. 1745:8–14, 1746:6–15. Accordingly, neither Pollyea nor Fowler inherently disclose crystalline Form A of ibrutinib.

7. Prior Art for Obviousness

a. Honigberg (DTX-278)

Honigberg discloses in its Figure 1 the chemical structure of PCI-32765 (i.e., ibrutinib). DTX-278 at -682; Tr. 600:21–601:1, 601:6–9. Honigberg discloses that

PCI-32765 was undergoing clinical trials in humans and had "shown promising clinical activity" as a "potent, selective and irreversible BTK inhibitor." DTX-278 at -685; Tr. 601:11–17. Honigberg does not identify any crystalline forms of ibrutinib or disclose the properties of crystalline forms or how to make them. Tr. 1705:5–21, 659:21–660:5; DTX-278

b. U.S. Patent No. 7,514,444 (the #444 patent) (DTX-1)

The #444 patent discloses the chemical name and structure of ibrutinib (referred to in the patent as "Compound 13") and a method of synthesizing ibrutinib. #444 patent at 4:4–6, 97:1–35. The #444 patent also discloses at least ten other BTK inhibitors by name, *see* #444 patent at 4:1–26 (naming compounds 4–6, 8–12, 14, and 15), and dozens more by structure, #444 patent at 36:30–51:37. The #444 patent discloses that BTK inhibitors such as ibrutinib may be used for the treatment of various diseases, including lymphoma. #444 patent at p. 1 (Abstract); Tr. 605:9–18.

The #444 patent states that the disclosed BTK inhibitors "*may* be in various forms," including in different crystalline forms. *Id.* at 60:38–49 (emphasis added). But the patent does not disclose that any crystalline forms of ibrutinib actually exist. The patent also teaches that [v]arious factors such as the recrystallization solvent, rate of crystallization, and storage temperature *may* cause a single crystal form to dominate." *Id.* (emphasis added). But the #444 patent does not provide

any guidance about which, if any, of these factors would apply to crystalline forms of ibrutinib.

c. Miller (DTX-1657)

Miller is a general reference on polymorphism. It does not mention ibrutinib or teach how to make crystalline forms of ibrutinib. Tr. 1707:24–1709:5, 653:4–654:19; DTX-1657. Miller gives a general introduction to crystal forms, crystal stability, crystallization, and polymorph screening. DTX-1657 at -759–60, -772–81; Tr. 552:32–553:1, 553:14–18.

d. Bauer (DTX-1008)

Bauer is a general reference on polymorphism. It does not mention ibrutinib or teach how to make crystalline forms of ibrutinib. Tr. 1707:24–1709:5, 653:4–654:19; DTX-1008. Bauer discusses polymorphism and matters related to polymorphism that should be considered during pharmaceutical development. DTX-1008 at 19–20; Tr. 555:7–11, 556:14–557:12. Bauer discloses that crystalline solids are usually highly stable and that most drugs are formulated using a crystalline form of the API for this reason. DTX-1008 at 16.

Bauer teaches that "[w]hich polymorph of a crystalline drug will form under certain conditions cannot be predicted." *Id.* at 18. It also teaches that studies to develop new crystalline forms require "crystallizing the drug from multiple

solvents of differing polarities, different solvent combinations, at different temperatures, at different rates of cooling, and other experimental conditions." *Id.*

8. Comparison of Claimed Limitations with the Prior Art

Claim 5 of the #455 patent claims crystalline forms of ibrutinib that have an XRPD pattern with 2-Theta peaks at six particular angles. Two of the prior art references—Honigberg and the #444 patent—disclose ibrutinib. But none of the prior art references disclose a crystalline form of ibrutinib, any XRPD data for crystalline ibrutinib, or how an artisan would crystallize ibrutinib generally or with the six claimed 2-Theta peaks.

9. Obviousness

Alvogen argues that the #455 patent is invalid for obviousness because an artisan of ordinary skill would have been motivated to combine the teachings of Honigberg, the #444 patent, Miller, and Bauer to achieve a crystalline form with the six claimed 2-Theta peaks and would have had a reasonable expectation of success in doing so.

a. Motivation

An artisan of ordinary skill would have understood from Bauer that crystalline forms of a drug were preferred over amorphous forms for solid oral dosage because they were more stable. That artisan would also have known from Honigberg that ibrutinib showed promising clinical results. Thus, I agree with

Alvogen that an artisan of ordinary skill would have been motivated to develop ***a*** crystalline form of ibrutinib.

But the inquiry is not whether an artisan would have been motivated to develop ***a*** crystalline form of ibrutinib; the inquiry is whether an artisan would have been motivated to develop crystalline ibrutinib having 2-Theta peaks at 5.7±0.1°, 13.6±0.1°, 16.1±0.1°, 18.9±0.1°, 21.3±0.1°, and 21.6±0.1°. *See KSR*, 550 U.S. at 418 (directing courts to consider an artisan's motivation to combine "the known elements *in the fashion claimed by the patent at issue*" (emphasis added)); *In re Cyclobenzaprine*, 676 F.3d at 1069 (directing courts to determine whether an artisan would have been motivated to "to achieve the claimed invention"); *Tris Pharma, Inc. v. Actavis Labs. Fl, Inc.*, 755 Fed App'x 983, 990 n.5 (Fed. Cir. 2018) (defendant must demonstrate a motivation to combine all the claimed limitations). And none of Alvogen's cited prior art references disclosed a crystalline form with any of the six claimed 2-Theta peaks, let alone suggested that a crystalline form with the six claimed 2-Theta peaks would be more desirable than any other crystalline form. Thus, none of these references would have motivated an artisan to develop a crystalline form of ibrutinib with the claimed 2-Theta peaks.

b. Reasonable Expectation of Success

As I found above, discovering new crystalline forms is challenging and unpredictable. While an artisan of ordinary skill might have had some expectation of finding a crystalline form of a compound, there is no predictability in producing a particular crystalline form before it is discovered. There are numerous variables in the crystallization process, but the prior art did not teach which variables would be key to crystallizing ibrutinib. *See, e.g.*, DTX-1008 at 18 (giving numerous variables for crystallizing drug compounds and stating that "[w]hich polymorph of a crystalline drug will form under certain conditions cannot be predicted"). As the prior art did not teach how to make any crystalline form of ibrutinib, an artisan of ordinary skill in June 2012 could not reasonably have expected to make a crystalline form of ibrutinib with the six claimed 2-Theta peaks.

c. Secondary Considerations

1) Unexpected Benefits

Crystalline Form A demonstrates excellent stability and the ability to be reliably manufactured on a commercial scale and formulated into a high-load tablet. Tr. 1711:17–1712:6. These properties—stability and the ability to be manufactured and formulated into a high load tablet—are not present in all crystalline forms. *Id.* And as Dr. Swift recognized, these properties made crystalline Form A an "ideal crystalline form" for pharmaceutical development. Tr. 596:15–597:4. The existence of Form A, let alone its highly desirable

properties, is nowhere suggested in the prior art. Tr. 1666:14–20. Thus, that Form A would have these desirable properties and be an "ideal" crystalline form was unexpected.

Alvogen suggests that these desirable properties were to be expected because stability and manufacturability are endemic to many of the most stable crystalline forms. D.I. 325 at 43 (citing D.I. 336 ¶ 201). But this argument requires that an artisan of ordinary skill to have understood that crystalline Form A was the most stable form at the time of the priority date. Because an artisan of ordinary skill would not have had that understanding, the unexpected stability and manufacturability of crystalline Form A support a finding of nonobviousness.

2) Copying

Numerous companies, including Alvogen, have sought to manufacture generic Imbruvica® capsules and tablets with crystalline Form A of ibrutinib, even though companies are not required to use Form A. Tr. 1712:13–24. Pharmacyclics argues that this copying demonstrates nonobviousness. Alvogen responds by suggesting that copying is due to a desire to show bioequivalence. D.I. 325 at 42 (citing *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (copying reference drug preparations "is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval")).

Although a generic manufacturer could show bioequivalence using a physical form of ibrutinib other than crystalline Form A, the evidence adduced at trial establishes that different physical forms often have different pharmacological properties. *See* Tr. 532:11–533:9; DTX-1008 at -2166 (different polymorphs "may or may not cause a difference in pharmacological effect (i.e., how the drug may work in the human body[])]"). Pharmacyclics has thus not shown that the copying is due to a desire to gain the benefits of the invention as opposed to a need to show bioequivalence. Accordingly, I do not find the other drug manufacturers' use of Form A in their generic products to be probative of nonobviousness.

B. Conclusions of Law

1. Anticipation

Alvogen argues that Pollyea and Fowler inherently anticipate claim 5 of the #455 patent because every lot of PCI-32765 used in the Phase I study was crystalline Form A of ibrutinib. D.I. 325 at 36–37. Alvogen argues that because crystalline "Form A *was the compound* in the Phase I study, the references necessarily disclose it." D.I. 325 at 37 (emphasis in the original). But the Federal Circuit rejected such an argument in *Endo Pharmaceuticals Solutions, Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1381–82 (Fed. Cir. 2018).[10]

[10] Although *Endo* considered inherency in the context of an obviousness analysis, I see no reason why its analysis would not be applicable in an anticipation analysis.

In *Endo*, prior art publications described clinical studies for a testosterone injection but did not disclose the specific formulation—called the vehicle formulation—used to deliver the testosterone that was later claimed in the patent. *Id.* 1377–78. The defendant in *Endo* argued "that the [claimed] vehicle formulation was 'necessarily present' in the [prior art publications] because it was later revealed to be the actual formulation the authors of the [publications] used in their reported clinical studies." *Id.* at 1381. The Federal Circuit disagreed. The court noted that although the prior art references disclosed pharmacokinetic performance data, the defendant had failed to prove by clear and convincing evidence that the pharmacokinetic data could only result from the claimed vehicle formulation. *Id.* 1381–82. Because a number of different vehicle formulations were possible, the court concluded that "a skilled artisan, reviewing the [publications], would not have necessarily recognized that the [publications'] authors used [the claimed vehicle formulation] for their reported clinical studies." *Id.* at 1382.

Alvogen has not offered such a reason. And in fact, the court in *Endo* cites caselaw from § 102 cases in its analysis. *See* 894 F.3d at 1381 (citing *In re Oelrich*, 666 F.2d 578, 581 (Fed. Cir. 1981)). Additionally, the Patent Trial and Appeal Board has applied *Endo* in an anticipation analysis. *See Amgen Inc. v. Alexion Pharms., Inc.*, No. IPR2019-00739, 2019 WL 4132683, *9–15 (PTAB Aug. 30, 2019).

In this case, Alvogen has not proven that a Phase I dose escalation study could only be conducted with crystalline Form A of ibrutinib. Because a Phase I dose escalation study could be performed with amorphous ibrutinib or one of its metastable polymorphs, "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 stud[y]." *Id.*

In short, since crystalline Form A was not necessarily present in Pollyea or Fowler, Alvogen has failed to prove by clear and convincing evidence that claim 5 of the #455 patent is invalid as anticipated under § 102.

2. Obviousness

As I found above, Alvogen has not shown by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine the teachings of the prior art to achieve the claimed crystalline form with the six claimed 2-Theta peaks and would have had a reasonable expectation of success in doing so. In addition to the lack of motivation and reasonable to expectation of success, the secondary consideration of unexpected results also supports a finding of nonobviousness. Accordingly, I conclude as a matter of law that Alvogen has not met its burden to establish that claim 5 of the #455 patent is invalid as obvious under § 103.

VI. THE #857 PATENT (THE TABLET FORMULATIONS PATENT)

The #857 patent is directed to pharmaceutical formulations of ibrutinib. Claims 30 and 37 claim high-load solid tablet formulations consisting essentially of ibrutinib and other ingredients at specific weight concentrations (% w/w) (claim 30) and ranges of weight concentrations (claim 37). #857 patent at claims 30, 37; Tr. 1798:23–1799:9. Alvogen argues that claims 30 and 37 are invalid for lack of adequate written description and for obviousness in light of the following prior art references: Imbruvica® Capsule Label; U.S. Patent Application Publication No. US 2013/0338172 (the #172 publication); an international patent application filed by Goldstein; and the Handbook of Pharmaceutical Excipients (HPE).

A. Findings of Fact

1. Artisan of Ordinary Skill

I find that an artisan of ordinary skill would have had a Ph.D. in pharmacy, chemistry, or chemical engineering, or a related field, with experience in industry or university in drug delivery and/or development of solid dosage forms; or a B.S. or M.S. in pharmacy, chemistry, or chemical engineering, or a related field, with more experience in industry or university in drug delivery and/or development of solid dosage forms. Alvogen's expert—Dr. Reza Fassihi—used a slightly different definition of an artisan of ordinary skill but testified that his opinions related to the #857 patent would not change if he had used the definition stated above. Tr. 259:9–24.

2. Priority Date

The #857 patent's priority date is March 3, 2015. D.I. 276-1 Ex. 1, ¶ 81.

3. Tablets Generally

Ingredients in solid dosage pharmaceutical formulations—e.g., tablets or capsules—are generally classified as either an active pharmaceutical ingredient (API) or an excipient. Tr. 255:18–24. An API is an ingredient that is intended to bring about a pharmacological or therapeutic effect. Tr. 251:18–20. Excipients, or inactive ingredients, assist in the manufacturing process or delivery of the active ingredient to a patient. Tr. 256:1–7. Excipients in tablets commonly serve as fillers, binders, glidants, lubricants, disintegrants, and surfactants. Tr. 1155:9–14.

4. Claims 30 and 37

Claim 30 reads:

> The high-load solid tablet formulation of claim 1, 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.

#857 patent at claim 30. Claim 1, from which claim 30 depends, requires the inactive excipients of claim 30 to be pharmaceutically acceptable excipients. #857 patent at claim 1.

Claim 37 reads:

> The solid tablet formulation of claim 27 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 at claim 37. Claim 27, from which claim 37 depends, requires the amount of ibrutinib to be between about 70 mg to about 840 mg. #857 patent at claim 27. The patent's written description explains that the phrase "consisting essentially of" (which appears in both asserted claims) means "excluding other elements of any essential significance to the combination for the intended use, but not excluding elements that do not materially affect the characteristic(s) of the compositions . . . ." #857 patent at 26:28–33.

5. Written Description

The written description of the patent recites verbatim the formulations claimed in claims 30 and 37, describes them as being for high-load solid tablets,

and characterizes them as embodiments of the invention. #857 patent at 43:47–44:6. It then goes on to state that in some of those embodiments, the ibrutinib dosage can be between 35 mg and 840 mg. #857 patent at 45:32–37. The written description also discloses an ibrutinib tablet formulation (BK21A) that satisfies every limitation of claims 30 and 37. #857 patent at tbl. 1F. The written description does not provide fixed amounts for the ingredients of the BK21A formulation but instead, as in the case of the formulations recited in claims 30 and 37, describes the ingredient amounts by their respective weight concentrations. *Id.* Later, the written description describes experiments conducted with ibrutinib tablets using the BK21A formulation ratios in 140 mg and 560 mg doses. *Id.* at tbls. 7, 8. That the inventors were conducting studies with tablets using the BK21A formulation would have conveyed to an artisan of ordinary skill that the inventors were in possession of those tablets.

An artisan of ordinary skill would have also understood that the formulations in the #857 patent, including those using the BK21A ratios in 140 mg and 560 mg doses, could have been scaled to make a tablet with the full range of claimed ibrutinib amounts. Tr. 1850:5–24. An artisan of ordinary skill could calculate the amount of each ingredient based on a desired ibrutinib dose or total tablet weight. Tr. 1850:5–24, 1219:24–1222:16 (Dr. Fassihi testifying that "[c]alculation is calculation"). Tr. 178:14–179:4. I thus find that the written description would

have conveyed to an artisan of ordinary skill that the inventor had possession of the claimed subject matter.

6. Prior Art

a. Imbruvica® Capsule Label (DTX-1413)

Imbruvica® Capsule Label is the first approved label for Imbruvica® capsules. D.I. 276-1 Ex. 1, ¶ 224. The label lists the inactive ingredients in the 140 mg Imbruvica® capsule, including croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Tr. 1813:11–17, 1159:23–1160:3. The label does not provide the amount of each excipient or the total weight of the capsule. Imbruvica® Capsule Label does not mention tablets. Tr. 1814:1–10, 1159:23–1160:3, 1209:11–13.

b. The #172 Publication (DTX-1399).

The #172 publication is a patent application that issued as U.S. Patent No. 9,296,753, which was cited to the PTO during prosecution of the #857 patent. #857 patent at p. 2 (References Cited).

The #172 publication describes numerous ibrutinib dosage forms, including specific working examples. Tr. 1814:11–1815:18, 1818:23–1819:10; DTX-1399 ¶¶ 631–34. Example 10 (titled "Capsule Formulations") describes four different ibrutinib capsule formulations with various excipients, including microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate.

Tr. 1814:20–1815:6, 1162:4–15; DTX-1399 ¶¶ 631–32. Table 5 discloses the following four capsule formulations:

TABLE 5

Capsule Formulations								
	40 mg Capsule		140 mg Capsule		140 mg Capsule		200 mg Capsule	
Component	w/w %	mg/ cap-sule	w/w %	mg/ cap-sule	w/w %	mg/ cap-sule	w/w %	mg/ cap-sule
crystalline Compound 1	29.6	40.0	60.9	140.0	42.4	140.0	74.1	200.0
Microcrystalline cellulose NF	57.4	77.5	23.0	53.0	45.9	151.4	8.5	23.0
Croscarmellose sodium NF	10.0	13.5	10.0	23.0	7.0	23.0	10.0	27.0
Sodium lauryl sulfate NF	3.0	4.0	6.1	14.0	4.2	14.0	7.4	20.0
Magnesium stearate NF	NA	NA	NA	NA	0.5	1.6	NA	NA

DTX-1399 ¶ 631, tbl. 5.

Example 11 (titled "Immediate Release Tablets") provides weight concentration ranges of ibrutinib and other ingredients for ibrutinib tablets. Tr. 1815:7–21; DTX-1399 ¶¶ 633–34. Example 11 identifies hypromellose, microcrystalline cellulose, lactose, and magnesium stearate as required ingredients, and croscarmellose sodium as an optional ingredient. Tr. 1162:19–1163:3, 1175:7–15, 1815:7–21; DTX-1399, ¶ 633. Example 11 describes tablets between 300 mg and 1,000 mg in weight, with ibrutinib up to 50% of the tablet weight. Tr. 1815:7–21; DTX-1399 ¶ 633.

TABLE 6

Components of Tablet Formulation

Ingredient	Range
crystalline Compound 1	5% to 50%
Hypromellose	2% to 10%
Croscarmellose sodium	0% to 15%
Microcrystalline cellulose	5% to 50%
Lactose	10% to 75%
Magnesium stearate	0.25% to 2.5%
Total	Tablet weight range: 300 mg to 1000 mg

DTX-1399 ¶ 633, tbl. 6.

c. Goldstein (DTX-985)

Goldstein is an international patent application that discloses ibrutinib formulations. Tr. 1812:12–20, 1163:6–14. Examples 2 and 3 are the only tablet formulations in Goldstein. Tr. 1812:23–1813:10, 1163:23–1164:11. The immediate release high-load tablet formulations of Examples 2 and 3 contain 80.9 percent and 60.98 percent ibrutinib, respectively. DTX-985 at -2036–37; Tr. 1164:22–1166:17. In addition to ibrutinib, Example 2 contains the following excipients and amounts: microcrystalline cellulose and/or lactose (collectively 8.1%), starch (7.3%), sodium starch glycolate (3.2%), magnesium stearate (0.3%), and silicon dioxide (0.2%). DTX-985 at -2036–37 (Example 2); Tr. 1163:6–1164:17, 1165:7–15. Example 3 contains the same excipients and amounts. DTX-985 at -2037; Tr. 1163:6–1164:17. Example 3 also includes hypromellose in its coating. Tr. 1164:12–1166:12; DTX-985 at -2036–37.

The inventors cited Goldstein to the PTO during the prosecution of the #857 patent. JTX-49 at 15224, 15284, 15288; Tr. 1203:15–1204:15, 1206:17–1208:10.

d. HPE (DTX-1625)

HPE is a general reference that provides the descriptions of pharmaceutical excipients. Tr. 1167:15–1168:5, 1054:25–1055:10, 1815:22–1816:11, 1816:18–22. HPE contains monographs for lactose monohydrate, microcrystalline cellulose, polyvinylpyrrolidone, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate, as well as "hundreds" of other excipients. Tr. 1815:22–1816:11, 1816:18–22, 1168:10–17; DTX-1625 at -2403 (microcrystalline cellulose), -2408 (colloidal silicon dioxide), -2411 (croscarmellose sodium), -2418 (lactose monohydrate), -2429 (magnesium stearate), -2432 (polyvinylpyrrolidone), -2439 (sodium lauryl sulfate).

HPE does not teach how to formulate any specific API. Thus, it teaches nothing about ibrutinib or its properties. Tr. 1816:12–17.

7. Comparison of Claimed Limitations with the Prior Art

The following chart depicts for each asserted claim and prior art reference the disclosed ingredients and their weight concentrations:[11]

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[11] Because HPE does not disclose an ibrutinib formulation, it is not listed in the chart. Similarly, excipients disclosed as being compatible with ibrutinib formulations but that are not part of a disclosed formulation are also omitted.

		#857 Patent		*Capsules*		*Tablets*	
		Claim 30	**Claim 37**	**Imbruvica® Capsule Label[12]**	**#172 Publication Example 10[13]**	**#172 Publication Example 11**	**Goldstein Examples 2, 3**
Claimed Ingredients	**Ibrutinib**	about 70%	about 69% to about 71%	Yes	42.4%	5–50%	80.9%
	Microcrystalline cellulose	about 5%	about 2% to about 5%	Yes	45.9%	**5–50%**	**0–8.1%**
	Lactose	about 14%	about 13% to about 15%	—	—	**10–75%**	0–8.1%
	Polyvinylpyrrolidone	about 2%	about 1% to about 3%	—	—	—	—
	Croscarmellose sodium	about 7%	about 6% to about 8%	Yes	**7.0%**	**0–15%**	—
	Sodium lauryl sulfate	about 1%	about 1% to about 4%	Yes	**4.2%**	—	—
	Silicon dioxide	about 0.5%	about 0.4% to about 0.6%	—	—	—	0.2%
	Magnesium stearate	about 0.5%	about 0.4% to about 0.6%	Yes	**0.5%**	**0.25%–2.5%**	0.3%
Unclaimed Ingredients	**Hypromellose**	—	—	—	—	2–10%	—
	Starch	—	—	—	—	—	7.3%
	Sodium starch glycolate	—	—	—	—	—	3.2%

[12] As noted above, Imbruvica® Capsule Label discloses the inclusion of the ingredient but does not set forth an amount or weight concentration.

[13] Although Example 10 contains four formulations, both parties emphasized in their respective findings of fact this particular formulation, which contains the same excipients as Imbruvica® capsules. *See* D.I. 336 ¶ 227; D.I. 332 ¶ 211.

As can be seen above, none of the prior art references teach the claimed amounts of ibrutinib; nor do any of the references disclose an ibrutinib formulation that uses polyvinylpyrrolidone.

The #172 publication's example 10 discloses croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate in amounts that fall into the claimed ranges but teaches a microcrystalline cellulose amount that is approximately nine times greater than the amount of ibrutinib recited in claims 30 and 37. Example 10 also does not teach the use of silicon dioxide or lactose in an ibrutinib formulation.

The #172 publication's example 11 discloses microcrystalline cellulose, lactose, croscarmellose sodium, and magnesium stearate in amounts that fall into the claimed ranges. It does not, however, teach the use of sodium lauryl sulfate or silicon dioxide in an ibrutinib formulation and it also contains hypromellose, which is not an ingredient recited in claims 30 or 37.

The Goldstein examples do not have the claimed amounts of lactose, silicon dioxide, or magnesium stearate and are missing croscarmellose sodium and sodium lauryl sulfate entirely. The examples described in Goldstein also contain the unclaimed ingredients starch and sodium starch glycolate. In fact, the only limitation of the claims that Goldstein teaches is the claimed amount of microcrystalline cellulose.

8. Obviousness

I now turn to whether Alvogen has shown by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success the claimed ingredients in their respective amounts to develop the claimed high-load solid tablet formulations of ibrutinib.

a. Motivation

Alvogen identifies in its posttrial briefing a single source of motivation for a skilled artisan to combine the claimed ingredients in their respective amounts. In Alvogen's words: "Drawbacks of capsules provided motivation to develop ibrutinib tablet formulations." D.I. 325 at 47 (capitalization altered); *see also* D.I. 325 at 47 ("Disadvantages of formulating an API like ibrutinib in a capsule dosage form would have motivated a [skilled artisan] to pursue a tablet formulation prior to the priority date of the Tablet Claims."); D.I. 325 at 49 (arguing that "[t]he motivation to combine the[] [prior art] references [cited by Alvogen] is readily-apparent" because, "[h]aving the motivation to create ibrutinib tablets starting with the Imbruvica® [Capsule] Label, the [skilled artisan] would look to the [#]172 [p]ublication and Goldstein because they describe specific ibrutinib *tablet* formulation examples." (underlining added; italics in the original)). Alvogen did not, however, adduce at trial any evidence, let alone clear and convincing evidence, that a skilled artisan perceived any such drawbacks as of the priority

date. Alvogen alleges that the Imbruvica® capsule's 140 mg size made it "inconvenient for patients" because they had to take four capsules to obtain the recommended 560 mg dose. But it introduced at trial no evidence of patients feeling inconvenienced by Imbruvica®'s dosing regimen as of the priority date or of skilled artisans perceiving at that time that patients were inconvenienced by or failed to comply with the prescribed regimen. Alvogen also alleges that "[c]apsules can also be less stable" than tablets. D.I. 325 at 47. But it offered at trial no evidence that Imbruvica® capsules exhibited any instability or moisture loss. And the record evidence of humidity and moisture stability testing adduced by Pharmacyclics showed that the Imbruvica® capsule's stability was not affected by heat, humidity, or moisture. JTX-489 at 19; Tr. 1819:19–1820:13. I find therefore that Alvogen failed to meet its evidentiary burden to establish that an artisan would have been motivated to combine the cited prior art references to achieve the claimed invention.

b. Reasonable Expectation of Success

Alvogen argues that an artisan of ordinary skill would have had a reasonable expectation of success in making the claimed high-load tablet formulation, since, in its words, "it would have been nothing more than routine optimization to develop the [tablet formulation] from the Imbruvica® [Capsule] Label with such additional excipients that were disclosed in the literature and vary the amounts of

excipients." D.I. 325 at 48. But Alvogen neither explains nor cites record evidence that shows what such "optimization" entails, which "routine" steps an artisan of ordinary skill would have pursued, or what variables an artisan of ordinary skill would have sought to "optimize[]." Tr. 1824:13–1825:5.

In any event, I find that Alvogen's cited references would not have provided a skilled artisan a reasonable expectation of success in developing the claimed tablet formulation. Considered alone or in combination, the references do not teach the ingredients and amounts recited in claims 30 and 37. A skilled artisan who studied the references as of the priority date would have been faced with a hodgepodge of teachings of capsules and tablets, with different excipients and different amounts, and no reason to pursue a formulation with the specific ingredients recited in the asserted claims.

None of Alvogen's cited references teaches the claimed amount of ibrutinib, microcrystalline cellulose, or lactose; nor does any reference disclose an ibrutinib formulation using polyvinylpyrrolidone, about 0.5% silicon dioxide, or about 1% sodium lauryl sulfate. Goldstein's high-load tablets in Examples 2 and 3 do not contain any polyvinylpyrrolidone, croscarmellose sodium, or sodium lauryl sulfate—all of which are required by claims 30 and 37. And Examples 2 and 3 contain starch and sodium starch glycolate—neither of which is present in the asserted claims. Goldstein's tablets contains ibrutinib, but in an amount (80.9%

w/w) that differs significantly from the amounts of ibrutinib recited in claim 30 ("about 70%") and claim 37 ("about 69% to about 71%"). #457 patent at claims 30 and 37; DTX-985 at -2036–37. Example 11 of the #172 publication describes an ibrutinib tablet formulation that lacks the claimed ingredients of polyvinylpyrrolidone, sodium lauryl sulfate, and silicon dioxide. It also contains hypromellose, which is not present in claims 30 and 37; and it uses 5–50% ibrutinib, rather than 70% (or 69–71%).

Alvogen's expert, Dr. Fassihi, opined that a skilled artisan would have selected polyvinylpyrrolidone rather than (i) hypromellose (used in Example 11 of the #172 publication), or (ii) starch and sodium starch glycolate (both used in Examples 2 and 3 of Goldstein). But the prior art did not teach that polyvinylpyrrolidone was a better binder to use with ibrutinib than those or any other widely-used binders. And although Dr. Fassihi opined that a skilled artisan could find polyvinylpyrrolidone in a list of binders in the #172 publication, that list also includes hypromellose, starch, and other binders that are not recited in the asserted claims. *Id.*; DTX-1399 ¶¶ 444, 453; Tr. 1869:25–1870:17.

Accordingly, I find that Alvogen has failed to establish by clear and convincing evidence that a skilled artisan would have had a reasonable expectation of success in formulating the claimed tablet formulation.

c. Secondary Considerations

Pharmacyclics argues that three objective indicia support a finding of nonobviousness: (1) Alvogen's copying of the Imbruvica® tablet formulation that embodies the claimed tablet formulations; (2) skepticism in the pharmaceutical industry that ibrutinib could be formulated as taught by the asserted claims; and (3) the commercial success of Imbruvica® tablets.

1) Nexus

As an initial matter, Alvogen argues that I should ignore Pharmacyclics's evidence of copying and commercial success because Pharmacyclics failed to demonstrate that Imbruvica® tablets embody the asserted claims, and thus any copying or commercial success of Imbruvica® tablets is, according to Alvogen, not relevant to whether the claims are invalid for obviousness. D.I. 325 at 50.

I find, however, that all four strengths of Imbruvica® tablets (140 mg, 280 mg, 420 mg, 560 mg) meet the limitations of claims 30 and 37 and thus are commercial embodiments of the claims. Tr. 1803:18–1805:2, 174:16–25, 178:19–179:3, 209:12–25; JTX-337 at 1. Alvogen disputes this finding on the grounds that the claims "recite formulations 'consisting essentially of' certain excipients" and Pharmacyclics "failed to analyze the excipients in the Imbruvica tablet coating to determine whether they are of essential significance to the combination for the intended use, or materially affect the characteristic(s) of the compositions." D.I.

325 at 50–51. But Pharmacyclics elicited at trial credible testimony from Dr. Roland Bodmeier and Dr. Williams that the coating on Imbruvica® tablets does not materially affect their characteristics. *See* Tr. 186:14–16, 239:24–240:24, 1870:24–1871:11. Accordingly, I reject Alvogen's contention that Pharmacyclics failed to establish a nexus between Imbruvica® tablets and the cited objective indicia of nonobviousness.

2) Copying

Although Pharmacyclics adduced compelling evidence that Alvogen copied the Imbruvica® tablet's formulation, *see, e.g.*, Tr. 1845:7–17, 1847:15–22, 1803:18–1805:5, 194:13–195:8, 197:24–198:11, 201:6–202:10, 207:19–22, 209:12–25, 213:15–17; JTX-793 at 11; JTX- 638 at 4; JTX-134 at 3; JTX-337 at 1, I do not find Alvogen's copying to be probative of nonobviousness since a showing of bioequivalence is required for FDA approval of Alvogen's tablet formulation. *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

3) Skepticism

Pharmacyclics adduced at trial credible evidence that other pharmaceutical companies were skeptical that ibrutinib could be formulated as a 70% w/w tablet formulation with lactose as required by the claims. AbbVie, for example, questioned whether a target profile containing 70% w/w ibrutinib could be

developed. Tr. 1829:21–1830:9, 1754:12–1755:6 (one of the #857 patent's inventors testifying that AbbVie described the target profile as being "a very difficult project to be successful"). Janssen, another sophisticated pharmaceutical company, criticized the 70% w/w ibrutinib formulation requirement, as it believed a 60% w/w ibrutinib formulation would improve manufacturability. Tr. 1832:12–1833:4, 1839:19–1840:3; JTX-478 at 2. And Janssen was also skeptical that ibrutinib could be formulated with lactose because of ibrutinib's inclusion of a primary amine. Tr. 1831:1–14, 1235:4–10. As Pharmacyclics's expert, Dr. Robert O. Williams III, explained, when primary amines are formulated with sugars like lactose, a chemical reaction called a Maillard reaction can occur and degrade the drug. Tr. 1831:1–14. Janssen had concerns as of the priority date that such a reaction would cause stability problems during storage. Tr. 1831:18–1832:11; PTX-744 at 8. This evidence of actual skepticism by Janssen and AbbVie supports a finding of nonobviousness. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335 (Fed. Cir. 2016) ("If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness.").

Pharmacyclics also argues that Cai, a scientific reference, supports a finding of skepticism. Cai teaches that compounds with poor solubility (like ibrutinib) are often difficult to formulate "at very high drug loading (ca.>70%)" amounts. PTX-

715 at 1. But I agree with Alvogen that Cai does not discuss ibrutinib and there were already examples of ibrutinib tablets with "very high drug loading" (e.g., Goldstein Examples 2 and 3). In other words, Cai's general misgivings about high-load tablets with poorly-soluble APIs would not amount to skepticism in light of the specific examples of Goldstein.

4) Commercial Success

As noted in my discussion concerning the #090 patent, Imbruvica® tablets are a commercial success.

B. Conclusions of Law

1. Obviousness

I have already found as a factual matter that Alvogen did not prove by clear and convincing evidence that an artisan of ordinary skill would have been motivated to combine with a reasonable expectation of success the claimed ingredients in their respective amounts. This conclusion is bolstered by my findings regarding the secondary consideration of skepticism and commercial success.

Alvogen's arguments that skepticism and commercial success do not support a finding of nonobviousness are unavailing. Alvogen argues that Pharmacyclics's commercial success evidence is irrelevant because Pharmacyclics has not demonstrated nexus. But since Imbruvica® tablets are a commercial success and Imbruvica® tablets are an embodiment of the asserted claims, Pharmacyclics has

made a prima facie case of nexus. And instead of affirmatively demonstrating that this success is due to some unclaimed factor, Alvogen spends its briefing arguing that plaintiffs have failed to show that the success is not due to some unclaimed factor. *See* D.I. 325 at 54 ("Plaintiffs' only purported evidence . . . . Plaintiffs further have no evidence . . . . Plaintiffs have no evidence . . . ."). Because Alvogen failed to rebut Pharmacyclics's prima facie case of nexus, commercial success supports a finding of nonobviousness.

With respect to the secondary consideration of skepticism, Alvogen suggests that skepticism had to be publicly available before the priority date. *See* D.I. 325 at 51 n.35. But this assertion is contrary to the law. *See Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011) ("[I]t would be error to prohibit a . . . patentee from presenting relevant indicia of nonobviousness, whether or not this evidence was available or expressly contemplated at the filing of the patent application.").

But while commercial success and skepticism are probative of nonobviousness, I did not find Pharmacyclics's evidence of copying to be probative of nonobviousness. Nevertheless, a lack of one secondary consideration does not negate Alvogen's failure to prove motivation and reasonable expectation of success by clear and convincing evidence. Accordingly, I conclude as a matter

of law that Alvogen has failed to establish that claims 30 and 37 of the #857 patent are invalid as obvious under § 103.

2. Written Description

Alvogen's written description argument appears to be that because the claims describe the ingredient amounts by their relative weight concentration whereas the written description only describes examples of tablets that embody the claims with fixed dosage amounts of 140 mg and 560 mg the inventors have "claimed more" than they have invented. *See* D.I. 325 at 55. But the written description is not limited to tablets with ibrutinib dosages of 140 mg and 560 mg. The written description teaches that an artisan can vary the amount of ingredients in the tablets as long as the artisan keeps the relative weight concentrations the same. Thus, consistent with my factual findings made above, Alvogen has failed to prove by clear and convincing evidence that the #857 patent's disclosure did not reasonably convey to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. Claims 30 and 37 of the #857 patent are therefore not invalid for a lack of written description under § 112.

VII. CONCLUSION

For the foregoing reasons, I find that all the asserted claims of the asserted patents before me are not invalid and that Alvogen infringes each of the asserted claims.

The parties will be directed to submit a proposed order by which the Court may enter final judgment consistent with this Opinion.