IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CEPHALON, INC., *et al.*, Plaintiffs, v. SLAYBACK PHARMA LIMITED LIABILITY CO., *et al.*, Defendants.	Civil Action No. 17-1154-CFC **CONSOLIDATED**

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OPINION

April 27, 2020
Wilmington, Delaware

COLM F. CONNOLLY
UNITED STATES DISTRICT JUDGE

Plaintiffs Teva Pharmaceuticals International GmbH, Cephalon, Inc., and Eagle Pharmaceuticals, Inc. have sued Defendants Apotex Inc. and Apotex Corp., Fresenius Kabi USA, LLC, Mylan Laboratories Ltd., and Slayback Pharma LLC under the Hatch-Waxman Act, 35 U.S.C. § 271(e)(2)(A). Defendants seek to bring to market generic versions of Plaintiffs' Bendeka®, a drug indicated for the treatment of chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL). D.I. 1 ¶¶ 1, 12.[1] Plaintiffs allege infringement of U.S. Patent Nos. 9,265,831 (the #831 patent), 9,572,797 (the #797 patent), 9,144,568 (the #568 patent) and 9,597,399 (the #399 patent) by all defendants and infringement of U.S. Patent No. 9,572,887 (the #887 patent) by Slayback. Defendants have stipulated to infringement of the asserted claims with two exceptions outlined below. Defendants argue that all asserted claims of the asserted patents are invalid.

I held a seven-day bench trial, and, 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.

[1] All docket citations are to the docket for C.A. No. 17-1154 unless stated otherwise.

I. BACKGROUND

Plaintiffs sell Bendeka® under New Drug Application No. 208194. D.I. 1 ¶ 13. Eagle is the owner and assignee of the asserted patents and has listed them in connection with Bendeka® in the Orange Book maintained by the Food and Drug Administration (FDA). *Teva Pharms. Int'l GmbH v. Apotex Inc.*, No. 17-1164 (D. Del. 2017), D.I. 1 ¶¶ 27–35. Cephalon holds an exclusive license to the asserted patents and has assigned to Teva its rights under the license, including the right to sue for infringement. *Id.*, D.I. 1 ¶¶ 38–39.

Bendeka®'s active ingredient is bendamustine hydrochloride (referred to by the parties as bendamustine), a nitrogen mustard chemotherapy drug that was first developed in East Germany in the 1960s. D.I. 334 at 2; D.I. 364 ¶ 1.

In 2008, Cephalon launched the first U.S. bendamustine product, Treanda®. Tr. 403:18–22. Cephalon initially sold Treanda® in a lyophilized, or freeze-dried, form. Tr. 404:7–11, 1357:13–19. Lyophilized drugs must be reconstituted into an injectable liquid before they can be administered to patients. Tr. 404:7–18, 405:8–06:4. Aware that bendamustine's toxicity makes it potentially dangerous for medical staff to reconstitute the drug, Eagle began in 2009 to develop a liquid bendamustine formulation that ultimately became Bendeka®. Tr. 83:7–84:13, 86:3–19.

In November 2014, Cephalon launched its own liquid version of Treanda®. Tr. 981:25–82:2, 1657:10–11.

In 2015, Teva acquired Cephalon, Tr. 1660:10–14, and Cephalon thereafter commercialized Bendeka® as permitted by its exclusive license agreement with Eagle, PTX-0408; Tr. 1660:10–24, 1795:4–9.

On December 7, 2015, the FDA approved Bendeka®, D.I. 307-1 ¶ 152, and on January 27, 2016, Teva launched Bendeka®, DTX-0500; Tr. 984:17–85:23, 1006:6–07:5. Bendeka® subsequently received orphan drug exclusivity, a seven-year period during which the FDA is precluded from approving any other manufacturer's application to market the same drug to treat the same rare disease. *Eagle Pharm., Inc. v. Azar*, 2018 WL 3838265, at *1 (D.D.C. June 8, 2018), *aff'd*, 952 F.3d 323 (D.C. Cir. 2020); Tr. 1725:15–19.

In March of 2016, Teva stopped selling liquid Treanda®. DTX-0500_0001; Tr. 1623:7–8.

In July and August of 2017, Defendants each filed an Abbreviated New Drug Application (ANDA) with Paragraph IV certifications under § 505(j) of the Federal Food, Drug and Cosmetic Act to gain FDA-approval for the commercial manufacture, use, and sale of a generic version of Bendeka®. *E.g.*, D.I. 1 ¶ 15. In August of 2017, Plaintiffs filed these suits alleging that Defendants' ANDA filings with Paragraph IV certifications constituted acts of infringement. *E.g.*, D.I. 1.

These cases were consolidated for all purposes. *See* December 13, 2017 Order.

At trial, Plaintiffs accused all Defendants other than Slayback of infringing six formulation claims in two of the asserted patents: claims 2, 3, and 5 of the #831 patent; and claims 9 and 11 of the #797 patent. Plaintiffs also alleged infringement of six administration claims in four of the asserted patents: claims 11, 18, and 22 of the #568 patent and claim 15 of the #399 patent (by all Defendants); claim 13 of the #399 patent (by Apotex only); and claim 13 of the #887 patent (by Slayback only). Defendants countered that (1) the asserted formulation and administration claims are invalid for obviousness under 35 U.S.C. § 103; (2) the asserted formulation claims are invalid for indefiniteness under 35 U.S.C. § 112; (3) the asserted formulation claims are invalid for lack of enablement under 35 U.S.C. § 112; and (4) claim 9 of the #797 patent is invalid for lack of written description. Defendants stipulated that they infringe or induce infringement of each of the asserted claims with two exceptions: Apotex, Fresenius Kabi, and Mylan argue that (1) their ANDA products do not contain "a stabilizing amount of an antioxidant" as the asserted formulation claims require; and (2) they do not induce infringement of claim 9 of the #797 patent.

II. OBVIOUSNESS

A. Legal Standards for Obviousness

Under § 103 of the Patent Act, codified at 35 U.S.C. § 1 *et seq.*, 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 [POSITA] to which said subject matter pertains." 35 U.S.C. § 103. 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 Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007). "Were it otherwise 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 [i.e., the "secondary considerations" identified in *Graham*] 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 (and looking to avoid reversal by the Federal Circuit) is to treat *Graham*'s "invitation" to look at secondary considerations like a subpoena.

Obviousness is assessed based on the perspective of a POSITA 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 a POSITA] 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 a POSITA "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 from 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. 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 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." *KSR*, 550 U.S. 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 combing

certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 416.

B. Obviousness of the Asserted Formulation Claims

1. Findings of Fact

a. The Priority Date

The parties agree that the date of invention (i.e., the priority date) for the asserted formulation claims is January 28, 2010. Tr. 403:4–6, 1352:16–21, 2015:3–16; #831 patent at (60); #797 patent at (60).

b. Definition of the Relevant POSITA

The parties agree that a POSITA would have had the skills, education, and expertise of a team of individuals working together to formulate a liquid injectable drug product. Such a team would have included individuals with doctoral degrees in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, chemical engineering, biochemical engineering or related fields, with at least two years of post-graduate experience in developing liquid injectable drug products, or master's or bachelor's degrees in similar fields of study, with a commensurate increase in their years of postgraduate experience. Such a team also would have been familiar with a variety of issues relevant to developing liquid injectable drug formulations, including, among other things, solubility, stability, pharmacokinetics, pharmacodynamics, and other pharmaceutical characteristics. Such a team also

would have included persons with expertise in analytical chemistry, including the detection and measurement of chemical degradants. The team also would have had access to an individual with a medical degree with experience in treating patients with CLL and NHL. PDX-4-2; Tr. 562:1–63:6, 1036:7–37:11, 1353:6–20, 2014:22–15:2.

c. Content of the Asserted Formulation Claims

The asserted formulation claims teach a non-aqueous liquid composition that contains (1) bendamustine (or a pharmaceutically acceptable salt thereof); (2) about 5% to about 10% by volume of the solvent propylene glycol (PG); (3) the solvent polyethylene glycol (PEG); (4) one of the following ratios of PEG to PG: about 95:5, about 90:10, about 85:15, about 80:20, and about 75:25; and (5) a stabilizing amount of an antioxidant. #831 patent at claims 2, 3, 5; #797 patent at claims 9, 11. Two claims also specify components and quantities: (1) claim 11 of the #797 patent requires that "the antioxidant is thioglycerol or monothioglycerol,"[2] and (2) claim 5 of the #831 patent requires that "the bendamustine concentration is from about 25 mg/mL to about 50 mg/mL." Certain claims also recite stability limitations such as "less than or equal to 0.11% PG esters at about 1 month of storage at about 5°C." #831 patent at claims 2, 3, 5; #797 patent at claims 9, 11.

[2] Thioglycerol or monothioglycerol are used synonymously. Tr. 519:10–15.

d. Bendamustine, PEG, and PG

Bendamustine has two relevant functional groups at opposing ends of its chemical structure: a nitrogen mustard group and a carboxylic acid group. Tr. 422:23–23:13, 430:19–31:6, 1038:5–7.

Nucleophiles—such as water, PG, and PEG—degrade bendamustine at its nitrogen mustard group through reactions in which an aziridinium ring forms. Tr. 407:12–19, 564:10–66:12, 1038:13–21, 1043:23–46:12, 1381:11–18; DTX-0073 at 4:33–37; PTX-1010 at TEVABEND00296748. Compounds like PEG and PG that have hydroxyl (OH) groups also degrade bendamustine at its carboxylic acid group through a process called esterification where the carboxylic acid group reacts with the OH groups to form degradants called esters. Tr. 431:4–13.

When PEG is combined with bendamustine, a process called PEG oxidation accelerates the esterification reaction. Tr. 484:15–85:11, 1416:11–18:12; PTX-0669 at TEVABEND00294275; PTX-0623 at TEVABEND00289470. PEG thus causes more degradation at bendamustine's carboxylic acid group than the same amount of PG would cause. Tr. 1054:5–59:11; PTX-0999 at TEVAVEND00292131; PTX-0997 at TEVABEND00291955.

Because water causes bendamustine to degrade at its nitrogen mustard group, the prior art bendamustine formulations used a lyophilized (freeze-dried) form of bendamustine that required a human operator to reconstitute it using water

shortly before administering it to a patient. DTX-0094_0010; Tr. 404:7–18, 405:8–06:4, 408:17–09:1, 410:4–5, 1357:13–19. Reconstitution by human manipulation had two known disadvantages in 2010: it increased the risk of contamination, Tr. 406:16–20; and, because bendamustine is a cytotoxic compound, it posed a potential danger to the operator, Tr. 84:2–13, 406:23–07:3; DTX-0056_0001; DTX-0056 at 2:33–67; DTX-0094_0011.

e. Content of the Prior Art

Defendants argue that five prior art references would have motivated a POSITA to arrive at the asserted formulation claims with a reasonable expectation of success: Olthoff, Drager, Alam, Rowe, and Boylan. D.I. 378 at 31.

1) Olthoff (DTX-0094)

Olthoff, a 1983 East German patent, claimed a stable, non-aqueous liquid injection solution of between 25 and 100 mg/mL bendamustine dissolved in a solvent consisting of 100% PG. DTX-0094_0016; Tr. 448:20–25. Olthoff's objective was to "produce a stable and ready-to-use injection solution out of N[itrogen]-mustard compounds, avoiding the technical solution of a dry ampoule [i.e., lyophilization]." DTX-0094_0012; Tr. 409:18–10:5. Olthoff disclosed that bendamustine has "a[n] extraordinarily high chemical stability for the production of injection solutions in" monovalent alcohols, glycols and polyols. DTX-0094_0012; Tr. 410:6–11:8. Olthoff specifically proposed dissolving

bendamustine in "polyols, particularly 1,2-propylene glycol [i.e., PG]." DTX-0094_0014; Tr. 412:6–14. Polyols are another name for compounds that have multiple OH groups. Tr. 412:17–18, 413:11–13. Both PEG and PG are polyols. *Id.*

Olthoff's examples did not use an antioxidant. DTX-0094_0013, _0015; Tr. 1457:5–12.

In the decades between Olthoff's publication and the priority date, its formulations were never used. DTX-0073 at 2:19–29.

2) Drager (DTX-0073)

About 30 years after Olthoff was published, Drager, a U.S. patent, issued in 2013. Tr. 434:6–20; D.I. 307-1 ¶ 223. (Drager's priority date is September 25, 2008 making it prior art to the asserted formulation claims.) Like Olthoff, Drager described stable "liquid pharmaceutical formulations comprising bendamustine." DTX-0073 at 2:33–35, Abstract; Tr. 433:23–25. But Drager determined that the "results described in [Olthoff] were not reproducible." DTX-0073 at 2:62–64. Drager's data showed that bendamustine in 99% PG degraded almost completely after eight weeks at 25°C and more than 20% at 5°C after one year. DTX-0073 at Fig. 3; Tr. 1378:9–80:5. The reason for that degradation, according to Drager, was that (1) PG causes bendamustine to degrade at the nitrogen mustard group, DTX-0073 at 4:19–24, 4:33–37; Tr. 602:13–15, and (2) PG's OH groups cause

bendamustine to degrade at the carboxylic acid group through esterification, DTX-0073 at 5:12–14; Tr. 602:3–6.

As a solution to the degradation problem, Drager disclosed the use of aprotic solvents, i.e., solvents containing no OH groups, in a liquid bendamustine formulation. DTX-0073 at 3:21–25; Tr. 581:19–82:12. Drager showed that dissolving bendamustine in 100% DMA, an aprotic solvent, results in no degradation of bendamustine at the carboxylic acid group. DTX-0073 at Table II; Tr. 432:22–33:7, 435:11–36:9.

Drager also taught that protic solvents—i.e., solvents, including PEG and PG, that have OH groups—are acceptable to use with bendamustine but only when combined with aprotic solvents. DTX-0073 at 3:3–10, 3:36–48, 4:18–24; Tr. 601:11–17. Drager showed that the formulation containing 66% DMA and 34% PG is stable. DTX-0073 at Table II; Tr. 436:16–37:15.

3) Alam (DTX-0056)

Alam, a U.S. Patent issued on November 7, 1989, disclosed stable liquid formulations of cyclophosphamide, a compound that, like bendamustine, has a nitrogen mustard group. DTX-0056 at Abstract, 1:5–8; Tr. 422:3–9, 424:6–12. Alam tested cyclophosphamide's stability in mixtures of three polyols—PG, PEG and glycerol—and found that the formulation containing PEG and PG had "less degradation than the others." Tr. 424:2–25:5, 428:6–12, 1421:18–24; DTX-0056

at Tables 1–5. Alam disclosed using PG at a ratio of from about 10% to about 90% and PEG at a ratio of from about 90% to about 10%. DTX-0056 at 4:6–12; Tr. 425:6–14.

Bendamustine and cyclophosphamide have two structural differences that bear on how they degrade when they are mixed with PEG and PG. First, because cyclophosphamide does not have a carboxylic acid group, cyclophosphamide does not experience esterification, i.e., it does not react with compounds such as PEG and PG that have OH groups to form esters. Tr. 430:22–31:1, 1077:25–78:6. Second, in bendamustine, the nitrogen mustard group is attached to a benzene ring, while in cyclophosphamide, the group is attached to a phosphoramide. Tr. 1075:4–25. Because it is attached to a benzene ring in bendamustine, a POSITA would have expected nucleophiles such as PEG and PG to accelerate degradation at the nitrogen mustard group via the formation of an unstable aziridinium ring. Tr. 1037:19–41:16, 1058:12–17, 1060:2–9; PTX-0376 at JDG_BENDA_00002265; PTX-1010 at TEVABEND00296748. But in cyclophosphamide, the phosphoramide deactivates the nitrogen mustard group and cyclophosphamide consequently does not degrade by forming the aziridinium ring in a liquid formulation before administration. Tr. 1076:1–77:24; PTX-0991 at TEVABEND00290978; PTX-0993 at TEVABEND00291516.

Neither Alam nor Drager used an antioxidant in their exemplary or preferred

formulations. Tr. 1458:2–58:23.

4) Rowe, Handbook of Pharmaceutical Excipients (DTX-0160)

Rowe's Handbook of Pharmaceutical Excipients disclosed that PEG is susceptible to oxidation and that one can use an antioxidant to prevent such oxidation. DTX-0160_0011; Tr. 486:7–24.

5) Boylan (DTX-0063)

Boylan disclosed a list of "some of the most commonly used antioxidants in pharmaceutical injectable formulations" including monothioglycerol. DTX-0063_0019, 0020; Tr. 487:12–18. Boylan also disclosed usual concentrations for each of the listed antioxidants. DTX-0063_0020; Tr. 487:18–19. Monothioglycerol is FDA-approved. Tr. 340:20–23.

2. Conclusions of Law

I find that Defendants have not established by clear and convincing evidence that a POSITA would have had reason to combine the limitations recited in the asserted patents' formulation claims. Although Defendants persuaded me that a POSITA would have had reason to try to develop a non-aqueous liquid bendamustine formulation, they failed to establish by clear and convincing evidence that a POSITA would have used in that formulation the PEG and PG solvents, PEG:PG ratios, antioxidant, concentrations of bendamustine, or PG ester stability limitations recited in the asserted claims. I do not find Plaintiffs' evidence

of secondary considerations to establish nonobviousness, but I find Defendants' failure of proof with respect to *Graham*'s primary factors in this case to be dispositive and that therefore the formulation claims are not invalid under § 103.

a. Non-Aqueous Liquid Bendamustine Formulation

Every asserted formulation claim requires a non-aqueous liquid formulation. Due to bendamustine's instability in water, the prior art used a lyophilized form of bendamustine. Tr. 404:9–18, 1357:13–19. But, as discussed above, lyophilization had known disadvantages. To avoid lyophilization while still avoiding the use of water, a POSITA would have been motivated to create a non-aqueous liquid bendamustine product. In fact, as can be seen in Olthoff and Drager, other inventors sought to create non-aqueous liquid bendamustine formulations before the priority date.

b. Use of PEG and PG

The claimed non-aqueous liquid bendamustine formulations contain the solvents PEG and PG. Defendants argue that Olthoff, Drager, and Alam would have motivated a POSITA to use PEG and PG with bendamustine. D.I. 378 at 13, 16.

1) Olthoff and Drager

Viewed in isolation, Olthoff would have led a POSITA to use PEG and PG in a liquid bendamustine formulation. D.I. 378 at 13; DTX-0094_0014; Tr.

412:3–18, 413:4–13. Olthoff provided a short, finite list of solvent options that included PEG and PG. Specifically, Olthoff reported that bendamustine is stable in monovalent alcohols and polyols, DTX-0094_0012–13; Tr. 410:6–11:8, 1084:13–86:11; and the disclosure of "polyols" would have given a POSITA just three polyol options: PEG, PG, and glycerol, Tr. 413:4–13. Plaintiffs dispute that assertion, D.I. 371 at 20–23, but Plaintiffs' expert himself limited polyols to those three options in a patent application that he submitted in 2009, *see* DTX-0764_0011 ("Preferably the water soluble plasticizer is selected from the group consisting of polyols (glycerin [i.e., glycerol], propylene glycol, polyethylene glycols) . . . ."). His response when confronted with that disclosure at trial was: "Yes, but I didn't -- at that time I didn't know that I would be sitting here today." Tr. 1575:2–76:1. Moreover, while I agree with Plaintiffs that Olthoff would have taught a POSITA also to consider monovalent alcohols, D.I. 371 at 21, Plaintiffs only list four monovalent alcohols that a POSITA would have considered using with bendamustine, D.I. 361 ¶ 73. Olthoff thus would have left a POSITA with three polyols and four monovalent alcohols as options. By providing a finite list, Olthoff would have made using PEG and PG obvious to try because a POSITA would face only "a finite number of identified, predictable solutions." *KSR*, 550 U.S. 398 at 421.

Drager, however, teaches away from Olthoff's teaching of using polyols

such as PEG and PG alone with bendamustine. As noted, Drager determined that the "results described in [Olthoff] were not reproducible." DTX-0073 at 2:62–64, 3:1–2. And Drager's data showed that bendamustine in 99% PG degraded almost completely after eight weeks at 25°C and more than 20% at 5°C after one year. DTX-0073 at Fig. 3; Tr. 1378:9–80:5. As Plaintiffs' expert, Dr. Siepmann, credibly testified, a POSITA would have considered 20% degradation after just one year at 5°C to be "not good." Tr. 1379:25–80:5.

Drager disclosed combining bendamustine with aprotic solvents as a means of reducing such degradation. DTX-0073 at 3:3–10, 3:21–25; Tr. 581:19–82:12. Drager also allowed for combining bendamustine with a mixture of aprotic solvents and protic solvents, including PEG and PG. DTX-0073 at 3:3–10, 3:36–48, 4:18–24; Tr. 601:11–17. But Drager stated that the concentration of protic solvents should be kept at 90%—and preferably lower—to limit degradation. DTX-0073 at 3:49–4:25; Tr. 1393:3–22. Drager specifically showed that a formulation containing 66% DMA and 34% PG is stable. DTX-0073 at Table II; Tr. 436:16–37:15.

Defendants assert that Drager taught the use of aprotic solvents because they have no OH groups and that, therefore, Drager would have motivated a POSITA to use solvents with a low number of OH-groups. Tr. 431:20–23, 437:8–15. They argue that "[w]hile Drager claimed a formulation containing a polar aprotic solvent

(DMA) and a polar protic solvent (PG), a POS[IT]A would be motivated to remove DMA from the formulation because DMA has been known to cause problems in formulations." D.I. 379 ¶ 65; D.I. 378 at 14–15. According to Defendants, because DMA was the only aprotic solvent listed by Drager that is "used in FDA products," D.I. 378 at 15, a POSITA would turn to protic solvents like PEG that have a relatively low number of OH groups. D.I. 379 ¶ 67; D.I. 378 at 21.

Drager, however, teaches away from the use of only protic solvents. Therefore, Drager would not have motivated a POSITA to replace DMA with a low-OH protic solvent. Defendants and their expert conceded that neither Drager's disclosures nor its examples taught using exclusively protic solvents. Tr. 583:1–83:10, 1886:17–19. Instead, Drager taught the use of an *aprotic* solvent with bendamustine to avoid degradation by nucleophiles like PEG and PG. Moreover, Drager disclosed numerous alternative aprotic solvents that could potentially replace DMA. DTX-0073 at 3:9–14; Tr. 1395:7–14. And DMA was *not* the only aprotic solvent in an FDA-approved product. The prior art reference Strickley, for example, disclosed that the aprotic solvents NMP and DMSO had been commercially used. PTX-0569 at JDG_BENDA_00003311–14; Tr. 1390:19–24.

A POSITA in 2010 reading Olthoff and Drager thus would have found that Olthoff taught combining bendamustine with polyols including PEG and PG, but

that Drager taught away from using protic solvents, such as PEG and PG, alone with bendamustine. "Where the prior art contains apparently conflicting teachings (i.e., where some references teach the combination and others teach away from it) each reference must be considered for its power to suggest solutions to an artisan of ordinary skill . . . consider[ing] the degree to which one reference might accurately discredit another." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (internal quotation marks and citation omitted).

After considering the two references, I find that a POSITA would have credited Drager's data and conclusions over those in Olthoff. Drager expressly asserted that the "results described in [Olthoff] were not reproducible." DTX-0073 at 2:62–64. And Drager used high-performance liquid chromatography (HPLC) to make its determinations while Olthoff used thin-layer-chromatography (TLC). Plaintiffs assert, and Defendants do not dispute, that HPLC is more reliable than TLC because of its superior sensitivity and ability to resolve impurities. Tr. 1074:4–75:3, 1086:17–20, 1380:14–25, 1511:5–11. Moreover, in the decades between Olthoff's publication in 1983 and the priority date in 2010, Olthoff's formulations were never used, suggesting that POSITAs generally did not rely on Olthoff. DTX-0073 at 2:19–29. "The elapsed time between [Olthoff] and the [asserted] patent's filing date evinces that the [asserted] patent's claimed invention was not obvious to try." *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed.

Cir. 2013). Thus, a POSITA looking at Olthoff and Drager would have followed Drager's teaching not to use protic solvents such as PG and PEG alone with bendamustine.

2) Alam

Defendants also argue that Alam's disclosure of mixing cyclophosphamide with PEG and PG would have motivated a POSITA to use those solvents with bendamustine because both bendamustine and cyclophosphamide have nitrogen mustard groups. D.I. 378 at 16. But two structural differences between cyclophosphamide and bendamustine that effect how they degrade when they are combined with PEG and PG would have discouraged a POSITA from relying on Alam in formulating bendamustine. First, unlike bendamustine, cyclophosphamide does not have a carboxylic acid group and thus does not undergo an esterification reaction when it is combined with PEG or PG. Tr. 1077:25–78:6, 1421:1–5. Second, because the nitrogen mustard group in bendamustine is attached to a benzene ring, while in cyclophosphamide it is attached to a phosphoramide, cyclophosphamide degrades differently at the nitrogen mustard group than bendamustine does. Tr. 1077:4-1077:24; PTX-0991 at TEVABEND00290978; PTX-0993 at TEVABEND00291516. Defendants' expert, Dr. Pinal, did not point to any prior art references to support his contrary conclusion that "the nitrogen group in the two molecules are exactly the same." Tr. 423:7–13, 504:21–05:5.

I find therefore that a POSITA in 2010 would not have viewed cyclophosphamide as a relevant comparator for bendamustine reactions, Tr. 1078:7–11, and would not have considered Alam in formulating a stable bendamustine formulation, Tr. 1420:10–21:5.

* * * *

In sum, Defendants have not proven by clear and convincing evidence that Olthoff, Drager, and Alam would have motivated a POSITA to use PEG and PG to create a non-aqueous liquid bendamustine formulation. Although Olthoff taught using polyols such as PEG and PG with bendamustine, Drager teaches away from the use of protic solvents such as PEG and PG alone with bendamustine and a POSITA would credit Drager's teaching over Olthoff's. Moreover, a POSITA looking to solve the degradation problem in bendamustine would not have considered Alam in formulating a liquid bendamustine product because Alam concerned a compound that degrades differently than bendamustine when combined with PEG and PG.

c. Use of Claimed PEG:PG Ratios

Every asserted formulation claim requires a PEG:PG ratio that falls between 95:5 and 75:25. Defendants argue that the claimed PEG:PG ratios would have been obvious "in light of Alam's express disclosure of the entire range from 10:90 to 90:10." D.I. 378 at 19–20. But as explained above, the prior art would not have

motivated a POSITA to use PEG and PG in the first place. Also, even if a POSITA had chosen to use PEG and PG, it would not have relied on Alam because Alam concerned a compound that degrades differently than bendamustine in reaction to PEG and PG. Finally, the claimed formulations use more PEG than PG whereas Alam preferred using more PG than PEG, DTX-0056 at 4:6–12, and a POSITA in 2010 would have known that PEG would cause more degradation at bendamustine's nitrogen mustard group than PG due to PEG oxidation. Tr. 1054:5–59:11; PTX-0999 at TEVAVEND00292131; PTX-0997 at TEVABEND00291955. Thus, Alam did not make obvious the PEG:PG ratios recited in the asserted formulation claims.

d. Use of An Antioxidant

Every asserted claim requires an antioxidant and one asserted claim requires that the antioxidant be monothioglycerol. Assuming a POSITA had chosen to use a 90% PEG and 10% PG bendamustine formulation, that POSITA would have been motivated to curb PEG oxidation: a process in which PEG accelerates the esterification reaction. Tr. 484:15–85:11, 1416:11–18:12; PTX-0669 at TEVABEND00294275; PTX-0623 at TEVABEND00289470.

Defendants argue that Boylan and Rowe would have motivated a POSITA to solve the oxidation problem with an antioxidant. D.I. 378 at 22–23. They assert that Rowe taught a POSITA to inhibit the oxidation of PEG with the inclusion of a

suitable antioxidant and that Boylan taught using specific antioxidants, including monothioglycerol. D.I. 378 at 23; Tr. 486:7–24, 488:7–9, 505:11–06:7, 543:2–5; DTX-0160_0011; DTX-0063_0020. Defendants also note that monothioglycerol is "very commonly used," and is FDA-approved for injectable products. D.I. 378 at 23.[3]

Other prior art references, however, teach away from the use of antioxidants. *See* Tr. 1452:20–53:21; *Note for Guidance*, European Agency for the Evaluation of Medicinal Products, PTX-0629 at TEVABEND00290713, TEVABEND00290720 ("Antioxidants should only be included in a formulation if it has been proven [t]hat their use cannot be avoided."); *Pharmaceutical Preformulation and Formulation*, Interpharm, PTX-0391 at JDG_BENDA_00000415 (stating that antioxidant use "is now in decline" and that "[a] preferred method of preventing oxidation [over antioxidants] is simply to exclude oxygen"). Moreover, none of the four approved injectable products in the prior art that contained PEG included an antioxidant. Tr. 600:4–6, 1454:24–55:17; PTX-0722 (Ativan); PTX-0718 (Busulfex); PTX-0720 (Robaxin); PTX-0569 at JDG_BENDA_00003308 (VePesid). In addition, the

[3] Defendants also assert that Drager taught "the use of antioxidants in the formulation." D.I. 378 at 22. They did not, however, request a finding of fact on this point and none of Drager's preferred or exemplary formulations contained an antioxidant. Drager mentioned that the invention may include other excipients such as an antioxidant, DTX-0073 at 7:1−18, claim 5, but it did not encourage a POSITA to use an antioxidant.

liquid bendamustine examples in Defendants' prior art references do not include antioxidants: Olthoff's liquid bendamustine formulation with PG had no antioxidant, DTX-0094 at JDG_BENDA_00002313; Tr. 1457:5–12, and neither Alam nor Drager used an antioxidant in their exemplary formulations, Tr. 1458:2–58:23. Accordingly, I find that Defendants did not establish by clear and convincing evidence that the combination of Boylan and Rowe would have motivated a POSITA to use an antioxidant.

e. Use of the Claimed Bendamustine Concentrations

Claim 5 of the #831 patent requires a bendamustine concentration of "from about 25 mg/mL to about 50 mg/mL." DTX-0006_0009. Defendants argue that "[t]here was nothing special or unobvious about [that] concentration range" in view of the Treanda® Label and Olthoff. D.I. 378 at 25.

First, Defendants assert that the lyophilized Treanda® Label would have motivated a POSITA to use the claimed concentrations because a POSITA would have multiplied the 120 mg/m^2 dose for NHL patients disclosed in the lyophilized Treanda® Label, DTX-0848_0001, by the average body-surface-area of a human, 2.0 m^2, to get a 240 mg total dosage, D.I. 378 at 25–26. According to Defendants, the POSITA then would have placed that dose in a common vial size of either 5 mL or 10 mL to arrive at a concentration of either 24 or 48 mg/mL. D.I. 378 at 26. Defendants, however, offered no evidence establishing why a POSITA would have

combined a dosage for a lyophilized bendamustine formulation with a particular vial size when making a liquid bendamustine formulation.

Second, Defendants argue that Olthoff would have motivated a POSITA to reach the claimed concentration because "Olthoff disclosed and claimed [PG-only] liquid bendamustine formulations containing 'concentrations of 25 mg/m[L] to 100 mg/m[L],'" D.I. 378 at 25, and Olthoff disclosed that bendamustine's solubility in PG was very high, 125 mg/mL, D.I. 378 at 26. Defendants assert that "[w]hile the prior art did not disclose bendamustine's solubility in PEG, . . . solubility is an inherent (i.e. intrinsic) property" that can be discovered through routine testing, and given the high 125 mg/mL solubility in PG, a POSITA "would understand that by adding PEG to PG, the solubility would drop from 125 to a lower value, and that at ten percent PG and 90 percent PEG, it would be possible to make a solution with a concentration of 25 milligrams per milliliter." D.I. 378 at 26–27.

But as explained above, Defendants have not established a motivation to use PEG and PG in the first place. Thus, even assuming that a POSITA could have found bendamustine's solubility in PEG through routine testing, Defendants did not establish by clear and convincing evidence that a POSITA would have been motivated to conduct such testing. As Plaintiffs note, Defendants' expert "testified only that the POS[IT]A would have considered it 'possible' to dissolve 25 mg/mL bendamustine in 90:10 PEG:PG at room temperature, far short of establishing

motivation" to use PEG. D.I. 371 at 43.

Moreover, Defendants fail to explain why a POSITA would believe that bendamustine would have a lower solubility in PEG and PG as opposed to in PG alone based only on bendamustine's high solubility in PG. In choosing a concentration, a POSITA would have required that the bendamustine concentration remain below the formulation's bendamustine solubility limit so that the bendamustine would completely dissolve and dangerous precipitation would not occur. Tr. 591:19–92:7, 593:23–94:4, 1434:13–35:9, 1435:10–25, 1472:12–14; PTX-0667 at TEVABEND00293319. Because a POSITA would want to avoid such precipitation, it would likely not combine bendamustine with a 90% PEG and 10% PG formulation based on bendamustine's solubility in PG alone.

f. PG Ester Stability Limitations

Finally, certain asserted formulation claims contain a stability limitation, i.e., a maximum amount of degradants called PG esters that the composition can have after storage for a set time period at a set temperature. For example, claims 2, 3, and 5 of the #831 patent recite compositions having "less than or equal to 0.11% PG esters at about 1 month of storage at about 5°C." #831 patent at claims 2, 3, 5.

Defendants argue that the stability limitations are an inherent property because at least one obvious formulation in the asserted claims would naturally result in the required PG ester levels. D.I. 378 at 27. But "[t]o prove that a claim

limitation is inherent in the prior art, [the challenger] must show . . . [not only] that the limitation at issue is necessarily present, or the natural result of the combination of elements," but also that the combination of elements that naturally result in the limitation is "*explicitly disclosed by the prior art.*" *Par Pharm., Inc. v. Twi Pharm., Inc.*, 120 F. Supp. 3d 468, 473 (D. Md.), *aff'd,* 624 F. App'x 756 (Fed. Cir. 2015) (emphasis added) (internal quotation marks omitted); *see also* D.I. 378 at 28 ("*Once an embodiment is shown to be obvious*, any corresponding data can be used to show that the stability property is inherent." (emphasis added)). Because I find that the combination of elements that Defendants allege inherently result in the stability limitations is not obvious, such limitations are not obvious through inherency.

g. Secondary Considerations

The parties adduced at trial evidence of only one secondary consideration that bears on the formulation claims—commercial success. D.I. 371 at 79–80. Plaintiffs argue that "[s]ales of Bendeka® exceed $2 billion," and that "Bendeka® halted the downward trend in bendamustine sales, despite increasing competition." D.I. 371 at 79. But such evidence does not support a finding of nonobviousness. First, Bendeka® sells at a lower price than the prior art lyophilized Treanda® product. Tr. 1641:25–42:3, 1680:2–12, 1798:8–99:2. Second, Plaintiffs' cluster

of exclusivities has blocked others from entering the market.[4] Tr. 1723:24–26:1, 1730:3–7. "Where market entry by others was precluded . . . the inference of nonobviousness of the asserted claims, from evidence of commercial success, is weak." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) (internal quotation marks, alterations, and citations omitted).

* * * *

Although the evidence of commercial success does not support a finding of nonobviousness, I still find that Defendants have not shown by clear and convincing evidence that the prior art they cited would have motivated a POSITA to reach the claimed formulations. As discussed above, a POSITA would have credited Drager over Olthoff, and Drager teaches away from the use of protic solvents such as PG and PEG alone with bendamustine. Moreover, a POSITA would not have relied on Alam in formulating bendamustine. Finally, clear and convincing evidence does not show that a POSITA would have relied on Boylan and Rowe as motivation to use an antioxidant because of the references that teach

[4] Cephalon had an exclusive license from Fujisawa to develop bendamustine in the U.S. DTX-1230_0001, _0002, _0019; Tr. 1226:24–27:1, 1263:21–25, 1233:18–34:25. Also, in 2008, lyophilized Treanda® obtained seven years of orphan drug exclusivity (ODE) and an additional six months of pediatric exclusivity. Tr. 1723:24–26:1. Bendeka® also received ODE. *Eagle Pharm.*, 2018 WL 3838265, at *1. Thus, Bendeka® received seven years of exclusivity that would prevent generics from entering the market until 2022. Tr. 1723:24–26:1.

away from the use of antioxidants in injectable formulations. And the Treanda® Label and Olthoff would not have motivated a POSITA to reach the claimed concentrations.

C. Obviousness of the Asserted Administration Claims

1. Findings of Fact

a. The Priority Date

The parties agree that the priority dates for the asserted administrations claims are (1) March 20, 2012 for claim 22 of the #568 patent, and (2) July 10, 2012 for the remaining administration claims. D.I. 332; Tr. 2015:10-16.

b. Definition of the Relevant POSITA

The parties agree that a POSITA would have had the skills, education, and expertise of a team of individuals working together to develop a safe and effective administration protocol for a cytotoxic parenteral[5] drug product. Such a team would have included individuals with doctoral degrees in pharmaceutics, pharmaceutical sciences, pharmacology, pharmacokinetics, pharmacodynamics, or related fields, with at least two years of post-graduate experience in developing protocols for pharmaceutical administration, or master's or bachelor's degrees in similar fields of study, with a commensurate increase in their years of post-

[5] In the pharmaceutical field, "parenteral" typically refers to products that are administered by injection. Tr. 407:6–8.

graduate experience. Such a team would have been familiar with a variety of issues relevant to administering liquid injectable drug products, including, among other things, toxicity, solubility, pharmacokinetics, and pharmacodynamics. Such a team would have included at least one individual with a medical degree with experience in treating patients with CLL and NHL. PDX-2-4; Tr. 1112:4-20, 1293:22–94:9, 1233:1–17, 2014:22–15:2.

c. Content of the Asserted Administration Claims

The asserted administration claims recite methods of treating CLL or NHL[6] with a liquid bendamustine composition. #568 patent at claims 11, 18, 22; #887 patent at claim 13. Certain claims require administering the bendamustine composition on days one and two of a 21-day cycle for NHL, #568 patent at claim 18, or on days one and two of a 28-day cycle for CLL, #568 patent at claim 11. One claim requires a bendamustine dose of "about 25 mg/m^2 to about 120 mg/m^2." #887 patent at claim 13.

The asserted administration claims also specify administration times, the longest time being "about 15 minutes or less." *See e.g.,* #568 patent at claim 22; #887 patent at claim 13. They also specify administration volumes that are all 100 mL or less. *See e.g.*, #399 patent at claim 13. Finally, certain claims specify post-

[6] Two claims recite, more generally, a "method of treating cancer or malignant disease." #399 patent at claims 13, 15.

dilution bendamustine concentrations ranging from 0.05 mg/mL to 12.5 mg/mL. *See e.g.*, #568 patent at claims 11, 18.

d. Content of the Prior Art

Defendants argue that eight prior art references would have motivated a POSITA to combine the elements of the claimed administration with a reasonable expectation of success: Palepu 2011, the Treanda® Label, Preiss 1985, Preiss 1998, Schöffski 2000a, Schöffski 2000b, Barth, and Glimelius.[7] D.I. 378 at 53.

1) Palepu 2011 (DTX-0984)

Palepu 2011 is the published application that led to the asserted formulation patents. Tr. 546:25–47:17. The parties have stipulated that Palepu 2011 disclosed the formulations claimed in the asserted formulation and administration claims. D.I. 320 ¶ 6.

2) Treanda® Label (DTX-0993 and DTX-1202)

The Treanda® Label, published in April 2009, D.I. 307-1 ¶ 247, disclosed two FDA-approved liquid bendamustine composition dosing schedules: (1) for CLL, intravenous (IV) infusion at a dose of 100 mg/m^2 over 30 minutes on days

[7] Defendants also cite Olthoff to argue that the asserted administration claims were obvious, but the arguments regarding Olthoff were advanced only by Dr. Yates, an admitted non-formulator, and an expert that all Defendants but Apotex rejected. Tr. 918:11–17, 920:19–22:13. Dr. Yates is a professional witness with limited relevant experience who has testified repeatedly for Apotex. Tr. 908:17–13:12. I did not find his testimony credible and do not rely on it.

one and two of a 28-day cycle for up to six cycles, Tr. 648:3–9; DTX-0993_0001; DTX-1202_001; and (2) for NHL, IV infusion at a dose of 120 mg/m^2 over 60 minutes on days one and two of a 21-day cycle for up to eight cycles, DTX-0993_0001; DTX-1202_001; Tr. 648:3–9.

The Treanda® Label required the administration of Treanda® in a volume of 500 mL, Tr. 652:13–16; DTX-1202_002, with a post-dilution bendamustine concentration of 0.2–0.6 mg/mL bendamustine, DTX-0993_0002; DTX-1202_003; Tr. 652:21–23.

3) Preiss 1985 (DTX-0320; DTX-0985)

Preiss 1985 disclosed the results of a pharmacokinetic analysis of bendamustine. DTX-0320_0002; Tr. 658:25–59:2, 1119:18–20. A pharmacokinetic analysis is a preliminary study in which a new drug is administered to a small number of patients to determine the Cmax and area under the curve (AUC). The Cmax is the peak concentration of the drug in the bloodstream; the AUC is the patient's total exposure to the drug. Tr. 659:3–15, 847:8–24, 1114:2–7, 1120:18–25. Pharmacokinetic studies are not designed to assess a drug's safety. Tr. 724:7–12, 1120:8–25.

Preiss 1985 administered bendamustine intravenously for three minutes to seven patients with various cancers. DTX-0320_0002; Tr. 659:23–60:2, 723:16–24:3. Preiss 1985 administered an average total dose of 280 to 375 mg.

Preiss 1985 reported "only rather mild side effects" at those doses. DTX-0320_0006; Tr. 664:6–20, 1123:9–22.

4) Preiss 1998 (DTX-0991)

Preiss 1998 investigated bendamustine's clinical pharmacology and defined bendamustine's maximum tolerated dose (MTD) and dose limiting toxicities (DLT). DTX-0991_0002; Tr. 674:16–25. The MTD of a drug is a tolerable dose without severe or life-threatening toxicities; it differs from a recommended dose for clinical use. Tr. 1126: 9–11. DLTs are severe or life-threatening side effects. Tr. 674:23–75:1, 1126:12–23. Preiss 1998 administered bendamustine to more than 50 patients with various cancers. DTX-0991_002. Preiss 1998 was not designed to evaluate the safety of an infusion protocol. Tr. 730:22–31:1, 731:8–21.

Preiss 1998 administered three-to-ten-minute one-time infusions of bendamustine in doses ranging from 54 to 226 mg/m^2. It also administered three-to-ten-minute infusions on four consecutive days in doses ranging from 20 to 88 mg/m^2. DTX-0987_005. Preiss 1998 concluded that "only mild toxicity occurred even at high doses (> 200mg/m^2 b-hydrochloride per cycle)." DTX-0991_0004; Tr. 676:19–25. Preiss 1998 reported "disorientation" and a "vegetative neurotoxic effect" after the one-time infusions of 175 mg/m^2 and 215 mg/m^2 doses. DTX-991_0004, _0005.

5) Schöffski 2000a (DTX-0987)

Schöffski 2000a administered bendamustine over 30 minutes and compared its results to the three-to-ten-minute infusions disclosed in Preiss 1998. DTX-0987_0002,_0005; Tr. 678:4–14. Schöffski 2000a reported that some side effects from its 30-minute infusions were comparable to those observed with the three-to-ten-minute infusions in Preiss 1998. DTX-0987_0005,_0006; Tr. 678:10–79:5.

6) Schöffski 2000b (DTX-0988)

Schöffski 2000b administered 60 to 80 mg/m^2 of bendamustine in 30 minutes. DTX-0988_0001–03; Tr. 679:20–22. Schöffski 2000b observed side effects that were comparable to those observed in Schöffski 2000a. DTX-0988_0005. Schöffski 2000b's authors did not "observe confusion or other signs of neurotoxicity when giving the drug as a repeated 30-min i.v. infusion." DTX-0988_0005.

7) Barth 2010 (DTX-1004)

Barth suggested administering bendamustine in a solvent volume of 100 to 250 mL. DTX-1004_0005; Tr. 658:12–20, 681:21–83:8. Barth explained that

> [t]he 30-minute short infusion [of bendamustine] that is practiced in Germany can be readily achieved with infusion volumes of 100 to 250 m[L] 0.9% NaCl.
>
> It is unclear why the American prescribing information specifies 500 m[L] 0.9% NaCl or a final concentration of 0.2-0.6 mg/m[L] . . . . A short infusion with such volume is difficult to implement.

DTX-1004_0005; Tr. 682:9–83:2. Barth did not disclose any study or data. DTX-1004_0005; Tr. 1157:22–59:18.

8) Glimelius (DTX-0079)

Glimelius disclosed the administration of 5-Fluorouracil to treat colorectal cancer as an infusion lasting ten to 20 minutes using a 50 to 100 mL mini-bag. DTX-0079_0001, _0002. Mini-bags are small standard size bags. Tr. 554:2–9.

2. Conclusions of Law

Defendants did not establish by clear and convincing evidence that a POSITA would have been motivated to combine the prior art references to arrive at the claimed administrations with a reasonable expectation of success. Although the prior art would have motivated a POSITA to reach the claimed formulation, dose, and dosing schedule, and although Plaintiffs' proffered secondary indicia of nonobviousness were of little or no probative value, I find that the prior art would not have motivated a POSITA to reach the remaining claim limitations, and thus the claims as a whole are not obvious.

a. Formulation, Dose, and Dosing Schedule

The parties agree that Palepu 2011, the published application that led to the asserted formulation patents, disclosed before the priority date the formulations found in the asserted administration claims. D.I. 320 ¶ 6. But Plaintiffs argue that Defendants have not shown that a POSITA would have been motivated to select

Palepu 2011's formulations for the administrations recited in the asserted claims. D.I. 371 at 48. Palepu 2011 itself, however, established a motivation to use its formulations: it touted advantages of its disclosed formulations including "that they have substantially improved long term stability when compared to currently available formulations" and that they "are advantageously ready to use or ready for further dilution" and thus "[r]econstitution of lyophilized powder is not required." DTX-0984_0002 at [0007]; Tr. 889:8–90:3. It is undisputed that a POSITA would have wanted to use a stable and ready-to-use formulation as part of an improved administration method.

A POSITA also would have been motivated to combine Palepu 2011 with the Treanda® Label to come up with the claimed doses and dosing schedule. Palepu 2011 instructed administering its formulations in accordance with the Treanda® dosing schedule. DTX-0984_0004 at [0044]; Tr. 856:8–9. And the Treanda® Label taught similar doses and the same dosing schedules as those in the asserted administration claims. DTX-0993_0001; DTX-1202_0001; Tr. 654:18–21, 695:10–20. The required dose found in the claims is about 25 mg/m^2 to about 120 mg/m^2 and the Treanda® Label requires doses of 100 mg/m^2 or 120 mg/m^2. #887 patent at claim 13; DTX-0993_0001; DTX-1202_0001. Also, the dosing schedule recited in the claims is the same as the Treanda® Label's schedule: (1) for CLL, infusion on days one and two of a 28-day cycle, #568 patent

at claim 18; DTX-0993_0001; DTX-1202_001; Tr. 648:3–9; and (2) for NHL, IV infusion on days one and two of a 21-day cycle, #568 patent at claim 11; DTX-0993_0001; DTX-1202_001; Tr. 648:3–9.

That said, the asserted administration claims require administering each bendamustine dose in faster times, in lower volumes, and at higher post-dilution concentrations than the Treanda® Label requires. The question thus remains whether a POSITA would have been motivated to reach the claimed administration times, volumes, and concentrations.

b. Administration Times, Volumes, and Post-Dilution Concentrations

All asserted claims require administering bendamustine in 15 minutes or less, with some requiring ten minutes or less. All asserted claims also require administering bendamustine in a volume of 100 mL or less, with some claims requiring about 50 mL. Finally, all but one of the asserted administration claims require post-dilution bendamustine concentrations ranging from 0.05 to 12.5 mg/mL.[8]

Defendants argue that the claimed administration times were obvious under the Preiss and Schöffski studies; that the claimed administration volumes are

[8] Claim 13 of the #887 patent, the only claim asserted against Slayback, does not have a concentration limitation. D.I. 362 at 3.

obvious under the Preiss studies, Barth, and Glimelius;[9] and that the claimed post-dilution concentrations are obvious under the Preiss studies and the Treanda® Label. Defendants also contend that Eagle's post-invention statements corroborate Defendants' assertion that the Preiss studies would have motivated a POSITA to use shorter administration times, lower volumes, and higher concentrations.

1) The Preiss Studies

Defendants argue that the Preiss studies support a finding that the claimed administration times, volumes, and concentrations are obvious. First, Defendants argue that a POSITA would have been motivated to administer bendamustine in 15 minutes or less because Preiss 1985 and Preiss 1998 disclosed that administration of bendamustine in three-to-ten minutes was well-tolerated in humans and Schöffski 2000a and 2000b disclosed that the safety results of 30-minute bendamustine administrations were consistent with Preiss's three-to-ten-minute infusions. D.I. 378 at 39–40. Second, Defendants assert that the Preiss studies render the claimed volumes of 100 mL or less obvious because, although the Preiss references did not disclose a volume, a POSITA would have known based on Preiss's three-to-ten-minute time constraint and typical infusion rates that the

[9] Relying on the testimony of Dr. Yates, Defendants also cite Olthoff to argue that the claimed volumes were obvious. D.I. 378 at 43. As noted above, I did not find Dr. Yates's testimony to be credible and will not rely on it. Moreover, Olthoff's example bendamustine formulation did not use PEG and, as explained above, Drager discredited Olthoff's data. DTX-0094_0015; Tr. 923:14–24.

studies infused similar volumes. D.I. 378 at 42. Third, Defendants contend that Preiss rendered the claimed concentrations of 0.05 to 12.5 mg/mL obvious because Preiss 1985 likely used a concentration of 5.6 mg/mL. D.I. 378 at 46.

I find, however, that the Preiss studies would not have motivated a POSITA to reach the claimed administration times, volumes, or concentrations because (1) a POSITA would not have relied on the Preiss studies to determine a safe and effective infusion time, volume, or concentration for bendamustine, (2) subsequent prior art taught away from Preiss's three-to-ten-minute infusions, and (3) Defendants only hypothesize that the Preiss studies used volumes and concentrations similar to those in the claimed administrations.

a) A POSITA would not have relied on the Preiss studies to determine a safe administration.

As an initial matter, Preiss 1985 and Preiss 1988 were not designed to evaluate safety, and thus a POSITA would not have relied on the Preiss studies to determine a safe infusion time, volume, or concentration. Tr. 724:7–12, 730:22–31:1, 731:8–21. Moreover, the Preiss studies did not provide enough data points or information to allow a POSITA to rely on them for safety information. Preiss 1985 tested only seven patients with various cancers, DTX-320_0002; Tr. 723:16–24:3, 1122:20–22; it did not discuss how it collected side effect information, including the number or timing of observations, the side effects being

observed, or a grading system, Tr. 724:14–28:16; and it neither specified which of the seven patients in the study had side effects nor distinguished between IV and oral side effects, Tr. 728:8–20. A POSITA would not have concluded that side effects would not be present in a larger population, Tr. 1121:1–5, let alone the relevant population, Tr. 1122:20–23:8, based on a study that covered only seven patients with various cancers and offered no explanation of how the side effects were studied or which patients experienced the side effects. Preiss 1998 similarly tested patients with various cancers, Tr. 1125:24–26:1, and it did not disclose when the side effects it reported were monitored or how many times side effect information was collected from patients. Thus, a POSITA would not have relied on either Preiss study to determine the safety of a short bendamustine infusion. Tr. 1122:14–19, 1123:9–22.

In addition, the parties agree that the claimed administrations require repeated cycles, D.I. 378 at 38; D.I. 371 at 59, but the Preiss studies did not administer bendamustine in repeated cycles.[10] And according to Defendants' expert, "bendamustine therapy side effects result from . . . the number of cycles given" and "these side effects are typically more severe in subsequent cycles

[10] Defendants cited no reference that administered bendamustine in ten minutes or less in repeated cycles. Tellingly, Defendants' references that did administer bendamustine in repeated cycles all used 30-minute infusions. DTX-0987_0001; DTX-0988_0001; DTX-1004_0002, _0005; DTX-0848; PTX-0268.

because there are cumulative effects on bone marrow." Tr. 736:11–37:20. A POSITA would therefore not have relied on the Preiss studies to determine the safety of a short infusion of bendamustine administered in multiple cycles. Tr. 1133:7–11. Moreover, neither Preiss study administered bendamustine over two consecutive days as the claims require. Tr. 1129:12–20.

The Schöffski articles also would not have motivated a POSITA to rely on the Preiss studies to determine the safety of a short infusion time, lower infusion volume, or higher infusion concentration. Schöffski 2000a reported that it observed *some* side effects like those in Preiss 1998, but did not compare the overall incidence or severity of side effects in the two infusion protocols. DTX_0987_0006,_0007; Tr. 1138:21–39:19. Also, Schöffski 2000b stated that it observed similar side effects to those observed in Schöffski 2000a, not that it observed the same side effects as Preiss. And Schöffski 2000b stated that it did not "observe confusion or other signs of neurotoxicity when giving the drug as a repeated 30-min i.v. infusion," DTX-0988_005, while Preiss 1998 reported "disorientation" and a "vegetative neurotoxic effect," DTX-0991 at JDG_BENDA_00006920–21.

b) Subsequent prior art taught away from the Preiss infusions.

Subsequent prior art also would have dissuaded a POSITA from relying on the Preiss studies. A POSITA would not have stopped with Preiss 1985 and Preiss

1998; instead, it would have also considered later prior art references that used 30 to 60 minute infusions and a 500 mL volume. "Too often the obviousness analysis is framed as an inquiry into whether a person of skill, with two (and only two) references sitting on the table in front of him, would have been motivated to combine . . . the references in a way that renders the claimed invention obvious. The real question is whether that skilled artisan would have plucked [those references] out of the sea of prior art and combined [them]." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016).

The Preiss researchers themselves conducted later studies and recommended in subsequent papers an infusion of at least 30 minutes in 500 mL. DTX-0987_0001; DTX-0988_0001; PTX-0268; DTX-0982_0009; Tr. 1145:13–46:7. Preiss 2003—conducted by the same research group as Preiss 1985 and 1998—reported administration over 30 minutes in repeated cycles. PTX-0268; Tr. 1141:21–43:15. Moreover, the Ribomustin Monograph—which set forth the prescription information for the German bendamustine product Ribomustin and was developed by a company that employed scientists involved in the Preiss and Schöffski studies—recommended a 30 to 60 minute infusion in 500 mL because of local toxicity concerns. DTX-0982_009; Tr. 1143:17–44:13, 1144:14–45:5, 1146:8–54:4.

c) Defendants only hypothesize that the Preiss studies used the claimed volumes and concentrations.

Finally, Defendants only hypothesize that the Preiss studies used similar volumes and concentrations as those recited in the asserted claims. With respect to volume, Defendants assert that although the Preiss references did not disclose a volume, "[b]ecause administration time and volume are related," a POSITA would have known based on Preiss's three-to-ten-minute time constraint and typical infusion rates that the studies infused small volumes. D.I. 378 at 42 (citations omitted). With respect to concentration, Defendants contend that "Preiss 1985 administered bendamustine in a dose of 280-375 mg in a bolus, [i.e., a volume that the] evidence showed likely meant 50 or 100 mL," and diluting 280 mg in 50 mL would result in a concentration of 5.6 mg/mL. D.I. 378 at 46. Such speculations about Preiss's infusion rate and volume, however, are only based on "conclusory and unsupported expert testimony" and they do not support a finding of obviousness by clear and convincing evidence. *See TQ Delta, LLC v. CISCO Sys., Inc.*, 942 F.3d 1352, 1361 (Fed. Cir. 2019) ("In cases like *InTouch*, *ActiveVideo*, and *DSS*, we rejected obviousness determinations based on conclusory and unsupported expert testimony.").

Defendants have thus failed to establish by clear and convincing evidence that the Preiss studies support a finding that the claimed infusion times, volumes,

and concentrations were obvious. "Whether a skilled artisan would be motivated to make a combination includes whether he would select particular references in order to combine their elements," *WBIP*, 829 F.3d at 1337, and a POSITA in 2010 would not have selected the Preiss studies to determine a safe and effective infusion for a bendamustine formulation.

2) Barth and Glimelius

Defendants also argue that the administration volumes are obvious under Barth and Glimelius. They note that Barth recommended a 100 to 250 mL bendamustine infusion, D.I. 378 at 43, and that a "POS[IT]A would have known from Glimelius (DTX-0079) that minibags, [standard infusion bag sizes of 50 or 100 mL], were typically used for infusions of 10-20 min," D.I. 378 at 44 (citations omitted).

Barth and Glimelius, however, would not have motivated a POSITA to use the claimed volumes. First, Barth did not disclose any study or data; it only suggested hypothetical smaller volumes. DTX-1004_0005; Tr. 1159:10–18. And Barth's 100 to 250 mL suggestion did not cover the claimed volumes (all claims require 100 mL or less). DTX-1004_0005; Tr. 1159:3–16. Second, Glimelius did not disclose any bendamustine administration, Tr. 841:3–42:22, and the mere availability of a standard IV bag would not have given a POSITA motivation to use a bag that size. IV bags of 50 mL were available before the priority date, but

had never been used to deliver bendamustine. D.I. 371 at 58.

3) The Treanda® Label

Defendants also assert that the Treanda® Label would have motivated a POSITA to use the claimed post-dilution concentrations. They argue that the claimed concentrations are obvious as inherent because diluting the claimed doses disclosed in the Treanda® Label in the claimed volume of liquid necessarily would have resulted in the claimed concentrations of bendamustine, PG, and PEG. D.I. 378 at 44. But because I find that the claimed volumes are not obvious, it does not follow that the claimed concentrations are obvious as inherent. Defendants also state that "on the lower end of the spectrum, the [claimed] concentration falls within the 0.2-0.6 mg/mL concentration of the Treanda® Label." D.I. 378 at 45. But the Treanda® concentrations only cover a small portion of the claimed range of 0.05 to 12.5 mg/mL and thus they do not render the claimed concentrations obvious.

4) Eagle's Post-Invention Statements

Defendants further argue that, through post-invention statements, Plaintiffs admitted that the prior art taught that short infusions in lower volumes were safe and effective. Defendants point to the fact that Eagle relied on the conclusions from the Preiss studies when it told the FDA that its Bendeka® protocol was safe. D.I. 378 at 51.

It is true that, in support of its request for permission to test Bendeka®, Eagle submitted to the FDA a Detailed Review of Literature that relied in part on data from the Preiss and Schöffski references. DTX-1041_0175. The literature review stated: "Thus, the short duration infusion of bendamustine appears to be well tolerated in this study and a dose of 215 milligrams has been reported in the literature as the clinically tolerated dose for bolus administration of bendamustine." DTX-1041_0175. Later, Eagle made similar statements to the FDA when drafting its Investigator's Brochure to support its requested study that required administering the Bendeka® formulation in ten minutes. DTX-1061 at 14.

Eagle's submissions to the FDA, however, also contained non-public, non-prior-art tests and analysis Eagle had conducted to show those short-infusion protocols were safe to test in humans. DTX-1041_0025–26. And I find that Eagle's post-invention discussion of the prior art that is intermingled with its own non-public data that it developed in inventing the claimed administration does not show that a POSITA who did not have Eagle's non-public data would have relied on the Preiss studies. Conclusions drawn from a patentee's "disclosures to the FDA" risk being "distorted by hind-sight bias," especially here where the FDA submission was dated after the priority dates and thus was written "through the lens of what [the inventor] had invented." *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1377 (Fed. Cir. 2019).

In sum, Defendants failed to prove by clear and convincing evidence that a POSITA reading the Preiss and Schöffski studies, Barth, Glimelius, and the Treanda® Label would have found the claimed infusion times, volumes, and concentrations obvious.

c. Secondary Considerations

Plaintiffs offered at trial evidence of four secondary considerations that bear on the administration claims: skepticism, long-felt need, commercial success, and industry praise. I did not, however, find this evidence to be probative indicia of nonobviousness for the following reasons.

1) Skepticism

Plaintiffs argue that "industry participants" were skeptical of the claimed invention. D.I. 371 at 77. But the skepticism they cite was apparently held by a "couple of nurses, a pharmacist[,] and an oncology medical resident," DTX-0959_0001, and investors, D.I. 371 at 78. Such "lack of enthusiasm by a few is not equivalent to skepticism." *BTG Int'l Ltd. v. Amneal Pharm. LLC*, 923 F.3d 1063, 1076 (Fed. Cir. 2019).

Plaintiffs also contend that the FDA declined to allow testing of Eagle's IV push method of administration because of safety concerns. D.I. 371 at 78. But the IV push method is not the claimed invention; the invention is the ten-minute infusion and the FDA told Eagle to proceed with its ten-minute infusion study.

PTX-0746 at EGL-BENDEKA_00146354; Tr. 1691:3–14; *see also* PTX-0747 at EGL-BENDEKA_00146355 ("[Eagle] stated that they have decided not to evaluate the IV push method administration. [Eagle] will use 120 mg/m^2 over 10 minutes in their bridging study.").

2) Long-Felt Need

Plaintiffs also argue that Bendeka®'s shorter infusion addressed a "long-felt need to reduce chair time for chemotherapy, improving patient experience and allowing more patients to be treated." D.I. 371 at 79. The parties offered competing expert testimony on this point. I found credible only Defendant's expert, Dr. Thirman, who testified that Bendeka® does not meaningfully reduce chair time because patients receive IV fluids and other drugs simultaneously with the administration of Bendeka® and the administration of those fluids and other drugs lasts for much longer than 15 minutes. Tr. 188:20–89:9, 189:22–24, 1744:14–51:20, 1745:20–46:6, 1751:3–51:8, 1765:18–66:6, 1779:11–18; DTX-0968_0001. For example, Bendamustine is frequently administered with a drug called Rituxan that has an administration time of four to eight hours. Tr. 190:24–91:6, 191:2–6, 713:14–22, 1746:11–17, 1781:14–22.[11]

[11] Plaintiffs' expert, Dr. Agarwal, was not credible. He testified that, based on his experience in a "community-based cancer center," Tr. 1288:19, there were "always issues with the chair time" in the oncology field and that Bendeka® resolved the chair time need, Tr. 1304:7–05:19. My assessment of his lack of credibility was informed by the logic and credible nature of Dr. Thirman's testimony and also by

Dr. Agarwal's dissembling with respect to his billing practices (which might explain why he favored shorter chair times). Dr. Agarwal initially denied having any idea how his patients are billed for his work: "I mean, I'm not, I'm not the biller and I don't get paid by the amount I bill or anything. . . . My only concern is the patient's safety and that's all I care about. . . . I have no clue honestly about billing, billing procedures." Tr. 1339:15–21. He volunteered that "billing, which is a totally different department, I have no clue how they do it and I don't take a look at it. I don't even know how to look at it." Tr. 1340:15–17. And when asked how billing relates to infusion time, Dr. Agarwal claimed to have "no idea how the billing codes work with the infusion." Tr. 1344:13–17. But when asked by the Court if he was "paid by salary," Dr. Agarwal responded: "So the way it works is, what they [his practice group] wanted is eat what you kill. Basically, if I see more patients, I get paid more. If I work harder, I get more. If I work less, I get paid less." Tr. 1345:7–11. He then continued to explain the billing process in detail:

> So the way it works is, so we have like repeated billing codes for repeated business, which are from level one to level four, and that's very small. You just mark what billing code you want to put. These are being audited by McKesson and auditors, that you are not -- they look at our notes. They decide if the doctor is overbilling or underbilling with the code. We have another code for the new patient.
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> * * * *
>
> So they have like one to four levels of visit. Depending on how much time I spend with a patient, either from 15 minutes to 30 minutes, I can go from a level one visit to a level four visit and that's what I mark on that. I think it's level one to level five. Level five is a very complex visit where I spend an hour or more with a patient, and most of the visits are about level three or level four, but these patients that are going to see me, I just bill level 3 or 4 and then I submit the payment and that is taken care of by the billing and coding department.

Tr. 1345:19–46:1, 1346:13–23. Also, when Dr. Agarwal was asked if he was "familiar with a term called infusion billing," he responded "Yes." Tr. 1338:2–4.

3) Commercial Success

Plaintiffs further argue that Bendeka®'s commercial success is demonstrated by (1) the fact that "Bendeka® halted the downward trend in bendamustine sales, despite increasing competition," D.I. 371 at 79, and (2) "Teva's choice to license Bendeka® and pay Eagle a portion of the profit for each Bendeka® sale, when it could keep all profits from Treanda®," D.I. 361 ¶ 222. But such evidence does not support a finding of nonobviousness. Plaintiffs have not provided evidence to establish that Bendeka®'s sales and Teva's decision to license Bendeka® were linked to Bendeka®'s patented advantages as opposed to Bendeka®'s exclusivities. *See* D.I. 371 at 80 ("Eagle's patents expire shortly after Teva's pre-existing patents."); Tr. 1725:25–26:2 (stating that with the Bendeka® license, Teva has FDA exclusivity until 2022). Also, the "competition" that Plaintiffs cite consists only of Eagle's Belrapzo®—a drug that shares Bendeka®'s formulation, but lacks the short-infusion protocol. D.I. 361 ¶ 219. Because Eagle benefits from the sales of both Belrapzo® and Bendeka®, it may have an incentive to market Bendeka® over Belrapzo®, Tr. 1652:19–53:2, and thus any evidence that Bendeka® has higher sales has little if any probative value.

4) Praise

Finally, Plaintiffs argue that "Bendeka®'s patented advantages . . . have received industry praise." D.I. 371 at 81. In support of this assertion, they cite (1)

Veteran's Administration (VA) newsletter that highlighted the advantages of Bendeka® as compared to Treanda®, (2) a study that noted attributes of Bendeka® that drive Bendeka®'s usage, and (3) Fresenius Kabi's pre-litigation statement that Bendeka® reduced "[p]atient chair time" and that Bendeka® could "have higher pricing and still retain volume due to the benefits it offers." D.I. 371 at 81; D.I. 361 ¶ 226. Here again, I find such evidence to have at best marginal probative value. As an initial matter, the VA does not even use Bendeka®. Tr. 1777:1–78:16. Second, the study Plaintiffs cite was funded by Teva and provides no connection between the claimed limitations and industry praise. Tr. 1305:25–07:4. Third, Fresenius Kabi's statement merely lists reduced chair time as a fact and does not exhibit any praise related to the asserted claims.

* * * *

In sum, the secondary consideration evidence does not support a finding of nonobviousness. I still find, however, that the asserted administration claims are not obvious. Defendants have not shown by clear and convincing evidence that Palepu 2011, the Treanda® Label, Preiss 1985, Preiss 1998, Schöffski 2000a, Schöffski 2000b, Barth, and Glimelius would have motivated a POSITA to arrive at the claimed administrations with a reasonable expectation of success. A POSITA would not have been motivated to follow Preiss's three-to-ten-minute (and potentially lower volume and higher concentration) infusions because (1) a

POSITA would not have relied on the Preiss studies to determine a safe bendamustine infusion protocol, (2) subsequent prior art taught away from the three-to-ten-minute infusions, and (3) Defendants only guess that Preiss used similar volumes and concentrations to those claimed. Moreover, Barth and Glimelius would not have motivated a POSITA to administer bendamustine at lower volumes because (1) Barth only disclosed hypothetical volumes that did not even include the claimed volumes of 100 mL or less and (2) Glimelius did not involve bendamustine. Finally, the claimed concentrations are not obvious as inherent or under the prior art.

III. INDEFINITENESS

Defendants argue that the asserted formulation claims are invalid because they each require "a stabilizing amount of antioxidant"—a requirement Defendants contend is indefinite. D.I. 371 at 2.

A. Legal Standards for Indefiniteness

"[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). "Indefiniteness is a matter of claim construction, and the same principles that generally govern claim construction are applicable to determining whether

allegedly indefinite claim language is subject to construction." *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1319 (Fed. Cir. 2008), *abrogated on other grounds by Nautilus*, 572 U.S. at 901 (rejecting Federal Circuit's "insolubly ambiguous" standard for indefiniteness). As in claim construction, in making an indefiniteness determination, the district court may make "any factual findings about extrinsic evidence relevant to the question, such as evidence about knowledge of those skilled in the art." *See BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017). "Any fact critical to a holding on indefiniteness . . . must be proven by the challenger by clear and convincing evidence." *Cox Commc'ns, Inc. v. Sprint Commc'n Co. LP*, 838 F.3d 1224, 1228 (Fed. Cir. 2016) (alteration in original)).

B. Discussion

Defendants argue that "the claims recite a 'stabilizing amount' [of antioxidant] with no guidance, functional or otherwise, on what degree of stability is required to obtain some unnamed objective." D.I. 380 at 3. But this argument conflates (1) whether a given antioxidant amount improves bendamustine's stability with (2) the extent to which that given antioxidant amount improves stability. The written description defines a "stabilizing amount of antioxidant" as an amount that "increase[s] or enhance[s] the stability of the bendamustine in the compositions described herein," #831 patent at 3:49–54; Tr. 370:25–71:9. Thus,

the "objective" of the antioxidant amount is not "unnamed" but is instead "to increase or enhance the stability of the bendamustine in the compositions" described in the specification.[12]

Defendants argue that the term is indefinite because "[t]he specification does not explain how to determine whether stability has been 'increased' or 'enhanced.'" D.I. 378 at 3. But as Plaintiffs' expert, Dr. Siepmann, credibly testified, a POSITA would understand that a stabilizing amount of an antioxidant includes any amount that decreases the amount of bendamustine degradation after any time period and at any temperature. Tr. 1485:4–87:10, 1502:8–12. And the patents provide a POSITA with a method for measuring stability: using HPLC to compare the amount of overall bendamustine degradation with and without the antioxidant. Tr. 1485:14–86:11. Example 3 demonstrates that a POSITA would compare the amount of bendamustine remaining in the same formulation, stored under the same conditions, with and without the antioxidant, #831 patent at

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[12] Section 112(b) of Title 35 provides that "[t]he specification shall conclude with one or more claims[.]" This language makes clear that the specification includes the claims asserted in the patent, and the Federal Circuit has so held. *See Markman*, 52 F.3d at 979 ("Claims must be read in view of the specification, of which they are part"). The Federal Circuit and other courts, however, have also used "specification" on occasion to refer to the written description of the patent as distinct from the claims. *See, e.g.*, *id.* ("To ascertain the meaning of claims, we consider three sources: The claims, the specification, and the prosecution history."). To avoid confusion, I refer to the portions of the specification that are not claims as "the written description."

7:59–8:27; and the specifications describe measuring the remaining bendamustine using HPLC, *id.* at 2:26–44, 2:57–3:4, 4:22–26; Tr. 1487:11–89:11. In addition to providing exemplary test methods, the specification also lists "suitable antioxidant amounts" and "antioxidants," and provides examples of "stabilizing" amounts. #831 patent at 3:57–4:8, 7:59–9:2; Tr. 371:15–72:18, 1489:23–90:4.

In *BASF*, the Federal Circuit held the term "composition . . . effective to catalyze" not indefinite, even though the patent did not "recite a minimum level of function needed to meet this 'effective' limitation" or "a particular measurement method," because tests for determining whether a composition was catalyzing were well-known. 875 F.3d at 1366–68. Here, the term "stabilizing amount of antioxidant" is like the term "composition . . . effective to catalyze" and Plaintiffs' expert, like the expert in *BASF*, persuasively testified that a POSITA would know how to determine whether an amount of antioxidant is stabilizing. Moreover, unlike in *BASF*, the asserted patents here provide a test method.

Finally, Defendants cite the patentee's removal of antioxidant and stability limitations during prosecution as support for their indefiniteness argument. D.I. 378 at 5–6. But the removal of those limitations undercuts Defendants' argument because it confirms that the "examiner understood" the claims without those limitations. *See Sonix Tech. Co. v. Publ'ns Int'l, Ltd.*, 844 F.3d 1370, 1379–80 (Fed. Cir. 2017).

I thus find that the term "stabilizing amount of antioxidant" is not indefinite and I construe it as: any amount of an antioxidant that decreases the amount of bendamustine degradation after any time period and at any temperature.

IV. ENABLEMENT

Defendants assert that the asserted formulation claims are invalid for lack of enablement because the formulation patents disclosed neither the use of sodium hydroxide (NaOH) or of "other undisclosed variables." D.I. 378 at 59.

A. Legal Standards for Enablement

"Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013) (citation omitted). "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) (citations omitted). 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. *Abbott Labs.*, 720 F.3d at 1384 (citations omitted).

B. Discussion

Defendants argue that the asserted formulation claims are not enabled because the claims do not contain NaOH and "a pH adjuster like NaOH is necessary to obtain the PG ester levels claimed in the [a]sserted [f]ormulation [c]laims." D.I. 378 at 59. Defendants note that "Eagle's later-filed [#]879 application . . . explains [that] 'the control samples, which did not include NaOH did not provide long term storage stability,' and 'exhibited more than 28% total esters compared to initial after six months of storage at 25° C.'" D.I. 378 at 60 (citation omitted).

Evidence that some claimed formulations did not result in the PG ester limitations, however, does not establish that the claims are not enabled. Defendants have not presented any evidence to show that a POSITA would have had to undertake undue experimentation to alter the formulation to obtain the PG ester limitations. That some formulations with the claimed ingredients do not satisfy the PG ester limitations does not support non-enablement unless the number of such formulations is significant enough to have required a POSITA to experiment unduly. *See Atlas Powder*, 750 F.2d at 1576–77 ("Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. . . . Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to

practice the claimed invention, the claims might indeed be invalid. That, however, has not been shown to be the case here." (citations omitted)). Defendants presented no evidence showing that the number of unsuccessful formulations is significant enough to require undue experimentation. Accordingly, they failed to establish by clear and convincing evidence that the asserted claims are invalid for lack of enablement.

V. WRITTEN DESCRIPTION

Apotex argues that claim 9 of the #797 patent is invalid for lack of written description. D.I. 378 at 60. It asserts that "the absence of any mention of a pH adjuster like NaOH in the [#]797 patent demonstrates that the inventors did not have possession of it at that time, as confirmed by their later filing of another patent application that discloses and claims it." D.I. 378 at 61 (citations omitted). "But written description is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described . . . . " *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014). And Apotex never cites the intrinsic record to show that the asserted formulation patents claim something that they do not describe in their written descriptions. Instead, Apotex improperly cites extrinsic evidence—the later-filed Eagle patent application. Apotex has thus failed to establish that claim 9 is invalid for lack of written description.

VI. INFRINGEMENT

Defendants stipulated to infringement of the asserted claims with two exceptions. Apotex, Fresenius Kabi, and Mylan argue that (1) they do not infringe the asserted formulation claims because their ANDA products do not contain "a stabilizing amount of an antioxidant" as the asserted formulation claims require, D.I. 369 at 2; and (2) they do not directly infringe or induce infringement of claim 9 of the #797 patent, which requires that the "bendamustine-containing composition ha[ve] less than or equal to 0.43 % total PG esters at about 3 months of storage at a temperature of about 25°C," because their proposed labeling does not direct physicians to store their ANDA products for about 3 months at about 25°C, D.I. 369 at 4–5.

A. Legal Standards for Infringement

A defendant is liable for patent infringement if it files an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2)(A). To establish infringement based on the filing of an ANDA under § 271(e)(2)(A), a patentee must show that "if the drug were approved based upon the ANDA, the manufacture, use, or sale of that drug would infringe the patent in the conventional sense." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997).

"Conventional" infringement includes direct infringement and inducement.

35 U.S.C. § 271 (a), (b). Direct infringement requires that "every limitation set forth in a claim . . . be found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995) (citation omitted). Inducement requires a showing "that the accused inducer took an affirmative act to encourage infringement with the knowledge that the induced acts constitute patent infringement." *Microsoft Corp. v. DataTern, Inc.*, 755 F.3d 899, 904 (Fed. Cir. 2014) (citation omitted). A plaintiff can prevail on a claim of inducement only if it establishes direct infringement. *See Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 921 (2014) ("[I]nducement liability may arise if, but only if, there is direct infringement." (internal quotation marks, alterations, and citation omitted)).

A patentee must prove infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984). "A patentee may prove infringement by any method of analysis that is probative of the fact of infringement, and circumstantial evidence may be sufficient." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) (internal quotation marks and citations omitted).

B. Direct Infringement of the "Stabilizing Amount of Antioxidant" Limitation

The asserted formulation claims require a "stabilizing amount of an antioxidant," a term that I construed as any amount of an antioxidant that decreases

the amount of bendamustine degradation after any time period and at any temperature.

Defendants' ANDA products each contain 5 mg/mL of the antioxidant monothioglycerol, *see* PTX-0474 at APOLIQBENDA_ANDA_0005427 (Apotex); PTX-0486 at FK_BENDA_00003243, 3245 (Fresenius Kabi); PTX-0007 at MYLBEN_000248 (Mylan); Tr. 372:19–74:13, and the formulation patents' written description shows that 5 mg/mL of monothioglycerol is a stabilizing amount. The written description identifies "5 mg/mL to about 20 mg/mL" as a "preferable" stabilizing amount of antioxidant. #831 patent at 3:49–68; #797 patent at 3:55–66. The written description also identifies "thioglycerol (also known as monothioglycerol)" as a preferred antioxidant. #831 patent at 4:1–8; #797 patent at 4:6–16. Moreover, Example 3 demonstrates that adding "5 mg/m[L] of lipoic acid . . . as a stabilizing antioxidant" to 20 mg/mL of bendamustine in PEG decreased the amount of bendamustine degradation after 15 days at 25°C and 40°C as compared to the same formulation without an antioxidant. #831 patent at 7:59–8:27; #797 patent at 7:61–8:29; Tr. 371:15–72:18. Example 4 recites dissolving 50 mg/mL bendamustine in 90% PEG and 10% PG, and adding "5 mg/m[L] of [mono]thioglycerol, α-lipoic acid or dihydrolipoic acid," an amount that it describes as "a stabilizing amount of an antioxidant." #831 patent at 8:29–65; #797 patent at 8:32–66.

Circumstantial evidence can establish infringement; and here, the asserted formulation patents' disclosures that 5 mg/mL of an antioxidant (and specifically monothioglycerol) is stabilizing shows that the 5 mg/mL of monothioglycerol that Defendants use in their ANDA products decreases the amount of bendamustine degradation as compared to the same formulation without an antioxidant. Finally, Fresenius Kabi and Mylan represented to the FDA that 5 mg/mL monothioglycerol was sufficient to ensure that the amount of bendamustine in their ANDA products did not fall below specification limits. *See* PTX-0054 at FK_BENDA_00000543 (Fresenius Kabi); PTX-0201 at MYL-BEN_005258 (Mylan); Tr. 374:14–77:1.

C. Direct and Induced Infringement of Claim 9 of the #797 Patent

Claim 1 of the #797 patent recites a "method of treating leukemia, Hodgkin's disease, or multiple myeloma" comprising "administering" the specified "liquid bendamustine-containing composition." #797 patent at 12:43–46 (claim 1). Claim 9 recites the method of claim 1, wherein the "bendamustine-containing composition has less than or equal to 0.43% total PG esters at about 3 months of storage at a temperature of about 25° C." #797 patent at claim 9. Defendants stipulate that their ANDA Products have "less than or equal to 0.43% total PG esters at about 3 months of storage at a temperature of about 25° C," but contend that they do not directly infringe or induce infringement of claim 9 because their

proposed labeling does not recommend storing their ANDA Products for "about 3 months" at "a temperature of about 25° C." D.I. 307-4 ¶ I.a; D.I. 320 ¶ 3.

I find, however, that even though Defendants' labeling does not mention storage, Defendants' ANDA products directly and indirectly infringe claim 9 because the PG ester limitation does not require the user to store the products for three months at 25°C. Claim 9's PG ester limitation describes a characteristic of the claimed formula; it is not a method step and thus, does not require action to infringe. The claim does not recite testing for the PG ester limitation; it just describes a composition that would have less than 0.43% PG esters if one were to test for them after storing the composition for three months at 25°C.

Defendants' proposal to construe the PG ester limitation as a method step that requires actual storage under the specified conditions also fails because it "renders [claim 9] nonsensical." *See Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1255 (Fed. Cir. 2010) ("A claim construction that renders asserted claims facially nonsensical cannot be correct." (internal quotation marks and citations omitted)). Although claim 1 of the #797 patent requires the composition to have "less than or equal to 0.11% total PG esters at about 1 month of storage *at a temperature of about 5° C*," claim 9 requires the same composition to have "less than or equal to 0.43% total PG esters at about 3 months of storage *at a temperature of about 25° C*." #797 patent at 12:61–63 (claim 1), 13:22–25

(claim 9). Under Defendants' proposed construction, to infringe, the user would need to store the composition simultaneously at different temperatures, which is impossible.

Defendants therefore directly infringe and induce infringement of claim 9 of the #797 patent. With respect to direct infringement, Defendants agree that their products have less than or equal to 0.43% total PG esters after storing them for three months at a temperature of about 25°C and, other than with respect to a stabilizing amount of an antioxidant, they stipulated to direct infringement of the remaining limitations. D.I. 320 ¶ 3. With respect to induced infringement, Defendants will encourage others to administer their ANDA products through their proposed labels. Although Defendants' proposed labeling does not mention the claimed PG ester limitations, Defendants know "that [their ANDA products] meet all of the claim limitations and, through [their] proposed label[s], encourage[] patients to administer [their ANDA products] in a manner that infringes the claimed method." *Orexigen Therapeutics, Inc. v. Actavis Labs. FL, Inc.*, 282 F. Supp. 3d 793, 816 (D. Del. 2017), *rev'd in part on other grounds sub nom. Nalpropion Pharm., Inc. v. Actavis Labs. FL, Inc.*, 934 F.3d 1334 (Fed. Cir. 2019). "Whether the [user] who performs the method by administering the [products] knows that the [products] meet the [PG ester limitations] is irrelevant for the purposes of infringement." *Id.*

VII. CONCLUSION

For the foregoing reasons, I find that all asserted claims of the asserted patents are not invalid and that Defendants infringe and induce infringement of 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.