IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EAGLE PHARMACEUTICALS, INC., Plaintiff, v. SLAYBACK PHARMA LLC, APOTEX INC., and APOTEX CORP., Defendants.	Civil Action No. 21-1256-CFC-JLH

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OPINION

October 25, 2022
Wilmington, Delaware

COLM F. CONNOLLY
CHIEF JUDGE

This patent infringement case arises out of separate filings of New Drug Applications (NDAs) by Defendant Slayback Pharma LLC (Slayback) and Defendants Apotex Inc. and Apotex Corp. (collectively, Apotex) with the Food & Drug Administration (FDA) for approval to manufacture and sell bendamustine hydrochloride drug products based on data from bioavailability and bioequivalence studies contained in the approved labeling for Plaintiff Eagle Pharmaceuticals, Inc.'s BELRAPZO® (bendamustine hydrochloride) Injection, 100 mg/ 4 mL (25 mg/mL).

Eagle alleged in its Complaint that Defendants' submissions of their NDAs constitute infringement of claims 2 and 4 of U.S. Patent No. 11,103,483 (the #483 patent) pursuant to 35 U.S.C. § 271(e)(2)(A). Both claims cover a "ready to use liquid bendamustine-containing composition." Slayback and Apotex denied infringement and alleged as defenses that the #483 patent is invalid. Apotex also filed counterclaims seeking declarations that the marketing and sales of its proposed product would not infringe the #483 patent and that the #483 patent is invalid.

At the parties' request, I scheduled two days for a bench trial. The parties presented their respective cases on infringement on the first day of trial. The only

disputed infringement issue was whether Defendants' proposed products are "ready to use." The parties stipulated that "ready to use" means "able to be dispensed with minimal if any effort or preparation; prepackaged." Eagle's expert, Dr. Graham Sewell, admitted at trial that Defendants' proposed products were not prepackaged; Defendants' expert, Dr. Michael Brandt, provided compelling testimony that in my view established by more than a preponderance of the evidence that an artisan of ordinary skill would not be able to dispense Defendants' proposed products with minimal if any effort or preparation. Accordingly, I ruled from the bench at the conclusion of the first day of trial that Eagle had failed to meet its burden to establish infringement by a preponderance of the evidence. That finding made it unnecessary to address the validity of the #483 patent. Although at trial I orally made the findings of fact and conclusions of law required by Federal Rule of Civil Procedure 52(a)(1), I expand on those findings and conclusions here for the benefit of the parties. Because I write for the parties, I assume familiarity on the reader's part with the applicable statutory scheme and legal doctrines.

I. FINDINGS OF FACT

A. The Parties

1) Eagle is a Delaware corporation with its principal place of business in New Jersey. D.I. 102, Ex.1 ¶ 1. The asserted patent is assigned to Eagle. D.I. 102, Ex. 1 ¶ 13.

2) Slayback is a Delaware corporation with its principal place of business in New Jersey. D.I. 102, Ex. 1 ¶ 2.

3) Apotex Inc. is a Canadian corporation with its principal place of business in Canada. D.I. 102, Ex. 1 ¶ 3.

4) Apotex Corp. is a Delaware corporation with its principal place of business in Florida. D.I. 102, Ex. 1 ¶ 4.

B. Eagle's NDA Products

5) Eagle sells two liquid bendamustine-containing compositions in the United States: BELRAPZO® pursuant to NDA No. 205580, D.I. 102, Ex. 1 ¶ 27, and BENDEKA® pursuant to NDA No. 208194. D.I. 102, Ex. 1 ¶ 41. The FDA approved BELRAPZO® on May 15, 2018. D.I. 102, Ex. 1 ¶ 28. It approved BENDEKA® on December 7, 2015. D.I. 102, Ex. 1 ¶ 42. The #483 patent is listed in connection with BELRAPZO® in the FDA's Orange Book. D.I. 102 ¶ 3.

C. Slayback's NDA Product

6) By letter dated October 31, 2018, Slayback notified Eagle pursuant to 21 C.F.R § 314.52(c)(2) that Slayback was seeking FDA approval of NDA No. 212209 to market a bendamustine hydrochloride injection product. D.I. 102, Ex. 1 ¶ 52.

7) On March 16, 2022, the FDA tentatively approved Slayback's NDA No. 212209. D.I. 102, Ex. 1 ¶ 54.

D. Apotex's NDA Product

8) By letter dated August 16, 2021, Apotex notified Eagle pursuant to 21 C.F.R. § 314.52(c)(2) that Apotex was seeking approval of NDA No. 215033 to market a bendamustine hydrochloride injection product. D.I. 102, Ex. 1 ¶ 55.

9) On April 8, 2022, the FDA tentatively approved Apotex's NDA No. 215033. D.I. 102, Ex. 1 ¶ 58.

E. The Asserted Patent Claims

10) Eagle asserts claims 2 and 4 of the #483 patent. Claims 2 and 4 depend from independent claim 1.

11) Claim 1 recites:

> A ready to use liquid bendamustine-containing composition comprising: bendamustine, or a pharmaceutically acceptable salt thereof, wherein the bendamustine concentration in the composition is from about 10 mg/mL to about 100 mg/mL; polyethylene glycol; and a stabilizing amount of an antioxidant; the composition having less than about 5% peak area response of total impurities resulting from the degradation of the bendamustine, as determined by HPLC at a wavelength of 223 nm after at least 15 months at a temperature of from about 5° C. to about 25° C.

#483 patent at claim 1.

12) Claim 2 recites:

> The ready to use liquid bendamustine-containing composition of claim 1, wherein the antioxidant is lipoic acid, thioglycerol, propyl gallate, methionine, cysteine, a metabisulfite, sodium formaldehyde sulfoxylate, a

> phenol-containing aromatic compound, a phenolcontaining aliphatic compound, dihydrolipoic acid, or a mixture thereof.

#483 patent at claim 2.

13) Claim 4 recites:

> The ready to use liquid bendamustine-containing composition of claim 1, having less than about 5% peak area response of total impurities resulting from the degradation of the bendamustine, as determined by HPLC as a wavelength of 223 nm after at least 15 months at a temperature of about 25° C.

#483 patent at claim 4.

14) It is undisputed that Defendants' proposed products practice every limitation of the asserted claims except for the "ready to use" limitation.

F. The Parties' Witnesses

1. Eagle's Witnesses

a. Expert Witness: Dr. Graham Sewell

15) Dr. Sewell holds positions "in both senior management of hospital pharmacy, and as a senior academic" in the United Kingdom at DeMontfort University and the University of Plymouth. Tr. at 52:24–53:1; 53:23–54:2 (Sewell). He has a B. Pharm in pharmacy and a PhD in pharmaceutical sciences. Tr. at 53:13–17 (Sewell).

16) Dr. Sewell has dispensed at some point almost all drug products that are used in the United Kingdom. Tr. at 55:9–10 (Sewell). He has not dispensed bendamustine drug products. Tr. at 110:1–18; 111:8–10 (Sewell).

b. Fact Witness: Praveen Subbappa

17) Subbappa is Slayback's Head of Alliance Management. Tr. at 196:23–197:3 (Subbappa). He is Slayback's point of contact with the FDA. Tr. at 199:13–14 (Subbappa).

c. Fact Witness: Dr. Ripen Misri (by deposition)

18) Dr. Misri testified by deposition as an Apotex 30(b)(6) witness. Tr. at 225:18–25 (Misri).

2. Defendants' Witness: Dr. Michael Brandt

19) Dr. Brandt is a senior medical science liaison for Janssen Oncology in the leukemia and lymphoma space. Tr. at 236:4–5 (Brandt). He also is a clinical instructor and professor at various United States universities in their pharmacy departments. Tr. at 241:25–242:10 (Brandt). He received his Bachelor of Science in pharmacy from the University of Utah and his Doctor of Pharmacy (Pharm.D.) from the University of Washington. Tr. at 239:5–8 (Brandt).

20) Dr. Brandt has over 35 years of experience in practicing and teaching oncology pharmacy, and he has prepared and dispensed thousands of chemotherapy doses, including doses in liquid concentrate forms. Tr. at 245:18–22

(Brandt). He has dispensed BENDEKA® hundreds of times. Tr. at 238:18–21 (Brandt).

21) Dr. Brandt was a very credible witness and gave compelling testimony at trial. Tr. at 330:3–4. As I stated at trial: "I've had more than a dozen trials in the past year. And I think he was one of the most credible witnesses I've had testify. He was very measured. He was direct in his answer to all the questions. I [also] found his testimony to be inherently consistent." Tr. at 330:12–16.

G. The Artisan of Ordinary Skill

22) The parties stipulated and I therefore find that an artisan of ordinary skill

> 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 included skilled medical professionals that have experience in selecting, dispensing, administering cancer treatments including treatments for patients with chronic lymphocytic leukemia and indolent B cell non-Hodgkin's lymphoma. The medical professional would have a medical degree and several years of experience in the clinical development of drugs, including cytotoxic drugs those that are administered intravenously and are prescribed/ordered, dispensed and administered in a manner that is safe and appropriate for patient treatment. This team would further include individuals that are or have regular interactions with oncologists, pharmacologists, toxicologists, clinical oncology pharmacists, specialty pharmacists, oncology nurses, and the like.

D.I. 112.

H. The Dispensing of Defendants' Proposed Products Requires More Than Minimal Effort and Preparation

23) Drs. Sewell and Brandt essentially agreed at trial that the dispensing of a liquid concentrate bendamustine drug consists of the safe and effective preparation and provision of the drug in accordance with the applicable prescription to a healthcare provider for administration to the patient. *See* Tr. at 253:15–19 (defining dispensing as "all of the steps necessary between receiving the order or the prescription from the provider, to the point where that is physically given to the person who will be providing it – or who will be administering it to the patient.") (Brandt); Tr. at 62:1–5 (defining dispensing as "preparing or providing a pharmaceutical preparation in accordance with a prescription, normally from an

experienced oncology doctor or hematology doctor, in a way that delivers safe and effective therapy to a patient.") (Sewell).

24) It is undisputed, and I find as a matter of fact, that because bendamustine is highly toxic and any unprotected physical contact with it could harm the dispenser and the provider who administers the drug, the dispensing of Defendants' proposed products must take place in a clean room. *See* Tr. at 266:8–10 ("Under the OSHA guidelines, you need to have a hazardous drug cleaning room or dispensing room as Dr. Sewell showed on there.") (Brandt); Tr. at 104:25–105:2 (stating that bendamustine must be dispensed in the "correct facilities" which is a "[clean] unit") (Sewell); Tr. at 64:22–66:15 (describing the clean room); Tr. at 64:25–65:3 ("This is actually a shot of a clean room that I designed and built in the hospital at Plymouth. And it produces around 58 to 70,000 doses per year of cytotoxic or SACT medication.") (Sewell); Tr. at 69:6–10 ("You have to imagine that I'm using the clean room that I just described to you, but in order to prepare this, we had to use—I just wanted to show the manipulations, and they are easiest shown on a bench top. That precluded the use of any cytotoxic drug.") (Sewell); Tr. at 194:1–2 ("[Dispensing is] completed once the product has come out of the [clean] unit.") (Sewell).

25) In light of the toxicity of bendamustine and the fragility of cancer patients, even the slightest error in dosage amount or quality could cause

substantial harm to the patient. *See* Tr. at 64:14–17 ("[C]ytotoxic drugs have a narrow therapeutic window. There's very little difference between the dose that can effectively treat the disease and a lethal dose, or certainly a dose that can cause severe adverse affects.") (Sewell); Tr. at 276:11–13 ("[T]he difference between the dose necessary for safe and effective use in a patient and the dose that is toxic to the patient is very, very close to each other.") (Brandt).

26) It is undisputed, and I find as a matter of fact, that the dispensing of a liquid concentrate form of bendamustine involves *at least* the following: (1) inspecting the vial of the drug to ensure it does not contain any particulate matter, Tr. at 134:1–8, 134:23–135:3 (Sewell); (2) removing the vial's cap, Tr. at 81:8–9 (Sewell); (3) swabbing the vial's septum with alcohol, Tr. at 81:8–9 (Sewell); (4) inserting a venting pin into the vial to equilibrate its pressure, Tr. at 81:8–9 (Sewell); (5) inserting the needle of a syringe in the vial, Tr. at 81:13–14 (Sewell); (6) withdrawing the requisite volume of the drug into the syringe, Tr. at 81:13–14 (Sewell); (7) removing the syringe from the vial, Tr. at 131:23–132:5, 141:18–142:4 (Sewell); (8) inspecting the syringe to ensure it contains no air bubbles, Tr. at 81:15–16, 133:2–19 (Sewell); (9) adjusting the syringe's plunger if air bubbles are detected, Tr. at 81:15–16, 133:2–19 (Sewell); (10) verifying after adjusting the plunger that the syringe still contains the correct volume of drug, Tr. at 81:15–16 (Sewell); (11) transferring the drug from the syringe into a diluent bag, Tr. at

81:17–18 (Sewell); (12) thoroughly mixing the contents of the diluent bag, Tr. at 81:19 (Sewell); and (13) visually inspecting the diluent bag to ensure the absence of particulate matter and discoloration. Tr. at 81:19–23, 138:11–20 (Sewell).

27) Undisputed steps 8, 9, and 10 are not disclosed in the proposed labels for Defendants' proposed products. *See* DTX 15; DTX 19A.

28) Dr. Brandt credibly testified, and I find as a matter of fact, that the label "is the first, [but] certainly not the only document or publication that [a pharmacist] look[s] at when . . . dispensing a chemotherapy drug." Tr. at 261:14–20 (Brandt).

29) Dr. Brandt testified credibly, and I find as a matter of fact, that none of the undisputed steps in the dispensing process requires minimal effort or preparation. Each step must be performed with more than minimal effort and preparation because "[t]here's nothing minimal or trivial about compounding a highly toxic cancer chemotherapy." Tr. at 277:7–8 (Brandt). Each of these steps, if done incorrectly, can cause harm to a patient because of the small difference between an effective dose and a lethal dose. Tr. at 276:8–13, 277:13–14 (Brandt). This harm is amplified for these products because cancer patients are fragile, so even a slight adjustment in the treatment can cause significant harm. Tr. at 277:14–16 (Brandt).

30) I also find, based on Dr. Brandt's testimony, that the aggregate of the undisputed dispensing steps involves more than minimal effort and preparation.

31) Dr. Brandt testified, and I agree, that Dr. Sewell's characterization of the dispensing process is a "gross simplification of a very complex and serious process." Tr. at 258:9–10 (Brandt).

32) As I stated at trial, I find Dr. Brandt's testimony to be more credible than Dr. Sewell's testimony in part because, unlike Dr. Brandt, Dr. Sewell does not have experience in dispensing bendamustine drugs, Tr. at 331:16–17, and because "the real gist" of Dr. Sewell's testimony was "a comparison of reconstitution versus having a liquid concentrate." Tr. at 331:17–19. I do not find that comparison to be persuasive because the stipulated construction of "ready to use" does not require a comparison between lyophilized products and liquid concentrate products. The relevant question is whether dispensing liquid concentrate bendamustine products requires minimal if any effort or preparation, not whether dispensing those products requires less effort or preparation than dispensing lyophilized products.

33) Finally, Dr. Brandt testified, and I find as a matter of fact, that the dosing steps required for Defendants' proposed products are part of the dispensing process. Dr. Sewell testified that the dosing steps are a prerequisite to dispensing, not part of it. Tr. at 103:11–13 (Sewell). For the reasons noted above, I found Dr.

Brandt more credible than Dr. Sewell generally. But on this particular point, I found Dr. Brandt's testimony more credible for the additional reasons that Defendants' proposed products are packaged in a multi-dose vial—i.e., more than one patient can receive medication from the vial, Tr. at 187:15–21 (Sewell)—and because the parties agree that the dose varies for each patient. At its most basic level, "cytotoxic drugs are generally dosed according to body surface area" so a larger patient will receive a larger dose. Tr. at 72:10–11 (Sewell). But the dose can also vary based on kidney function, blood type, white blood cell count, how the patient is feeling, and many other factors. Tr. at 270:20–271:25 (Brandt); Tr. at 73:16–19; 74:3–6 (Sewell). The parties agree that sometimes these factors are known in advance, but sometimes they are not discovered until the patient arrives to receive the medication. Tr. at 271:8–16 (Brandt); Tr. at 73:20–74:6 (Sewell). That additional reason supports Dr. Brandt's testimony that dose modifications are part of the dispensing process and further supports my finding that dispensing Defendants' proposed products involves more than minimal if any effort or preparation. Tr. at 275:12–23 (Brandt).

I. Defendants' Proposed Products Are Not Prepackaged

34) Defendants' proposed products are not prepackaged. *See* Tr. at 121:15–19 ("Q. Okay. So the defendants' accused products are, in your opinion, not prepackaged as far as this [claim] construction goes, right? A. As far as a

POSITA would understand, yes, because they are not a specific dose for an individual patient.") (Sewell).

J. Defendants' Use of "Ready to Use" in FDA Filings

35) Defendants described their proposed products as "ready to use" in numerous documents, including their NDAs, filed with the FDA. None of those documents, however, provide a definition of "ready to use" or shed sufficient light on the meaning of the term such that it could reasonably be inferred from the documents that Defendants believed that their proposed products could be dispensed with minimal if any effort or preparation.

36) Eagle adduced no evidence at trial that shows or even suggests how the FDA defines, uses, or interprets drug applicants' use of the term "ready to use."

37) Accordingly, I find as a factual matter that Defendants' characterization of their respective proposed products as "ready to use" in FDA filings does not establish that their proposed products can be dispensed with minimal if any effort or preparation.

K. Dr. Brandt's Testimony Regarding Neulasta

38) Eagle argued at trial that "the most important admissions that Dr. Brandt gave were at the beginning when he said the only product he's identified as ready to use is Neulasta and it requires only a couple of manipulations of the drug product before they are done dispensing [it]." Tr. at 332:2–6. Eagle insists that it

is "not consistent" for Dr. Brandt to maintain that Neulasta is ready to use but Defendants' proposed products are not. Tr. at 332:25–333:1.

39) In fact, Dr. Brandt gave three examples of "ready to use" drug products at trial: Neulasta, EpiPen, and GVOKE.

40) EpiPen and GVOKE are "prefilled auto injector[s]" that can be administered by the patient without the help of a healthcare provider. To administer them, the patient need only "take [them] out of the container, take the lid off, and just literally jab" the injector into the body. Tr. at 252:21–252:5.

41) Neulasta is a brand name for pegfilgrastim, a medicine used to stimulate white blood cells in patients with cancer or who have been exposed to ionizing radiation medicine. Neulasta is dispensed as a prepackaged syringe with a single, six-milligram dose that can be administered by taking it out of its box, attaching the needle, and injecting it into the patient. Tr. at 252:13–17 (Brandt).

42) Defendants' proposed products are not prepackaged, are multi-dose, and must be dosed individually for each patient. Accordingly, I find that Dr. Brandt's testimony regarding Neulasta is not inconsistent with his testimony that the dispensing of Defendants' proposed products requires more than minimal effort and preparation.

II. CONCLUSIONS OF LAW

Under § 271(e)(2)(A), the filing of an NDA for a drug claimed in an Orange Book-listed patent or the use of which is claimed in that patent constitutes infringement. *See* 35 U.S.C. § 271(e)(2)(A); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678 (1990). Because "the allegedly infringing drug has not yet been marketed[,] . . . the question of infringement must focus on what the [] applicant will likely market if its application is approved, an act that has not yet occurred." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997).

Analyzing infringement involves two steps. The first step is to construe disputed patent terms consistently with how they would be understood by an artisan of ordinary skill. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). The second step is to determine whether the accused products or methods infringe the patent by comparing those products or methods to the construed claims. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The first step in the infringement analysis is a question of law; the second is a question of fact. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1565 (Fed. Cir. 1997). A patentee bears the burden of proving infringement by a preponderance of the evidence. *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984).

The only disputed infringement issue is whether Defendants' proposed products meet the "ready to use" limitation of the asserted claims of the #483 patent. The parties stipulated, and I therefore conclude as matter of law, that "ready to use" means "able to be dispensed with minimal if any effort or preparation; prepackaged." D.I. 42.

As discussed above, Eagle conceded that Defendants' proposed products are not prepackaged. Eagle also failed to establish by a preponderance of the evidence that Defendants' proposed products can be dispensed with only minimal if any effort or preparation. Accordingly, Eagle has failed to establish that Defendants' filing of their NDAs constituted infringement of the asserted claims of the #483 patent.