IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MILLENNIUM PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff,	)	
	)	C.A. No. 12-1011-GMS
v.	)	CONSOLIDATED
	)	
SANDOZ INC., et al.,	)	
	)	
Defendants.	)	
	)	

MEMORANDUM OPINION

I. INTRODUCTION

In this patent infringement action, the plaintiff Millennium Pharmaceuticals, Inc. ("Millennium") alleges that Abbreviated New Drug Applications ("ANDAs") filed by the defendants Sandoz Inc. ("Sandoz"), Accord Healthcare, Inc. ("Accord"), and Actavis LLC ("Actavis") (collectively, "the defendants") infringe claims 20, 31, 49, and 53 of U.S. Patent No. 6,713,446 ("the '446 patent").[1] (D.I. 1.[2]) The court held a four-day bench trial in this matter on November 4 through November 7, 2014. (D.I. 139–42.) Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity of the '446 patent, specifically whether the asserted claims of the '446 are invalid as obvious under 35 U.S.C. § 103. (D.I. 132, 133.)

[1] The parties filed stipulations dismissing allegations that the defendants infringed U.S. Patent No. 6,958,319 on November 3, 2014. (*See* D.I. 122; 123; 124.)

[2] All citations to the court's docket refer to Civil Action Number 12-1011-GMS.

II. BACKGROUND[3]

A. The Parties

1. Millennium is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 40 Landsdowne Street, Cambridge, Massachusetts.

2. Sandoz is a corporation organized and existing under the laws of the State of Colorado, with its principal place of business at 56 Carnegie Center, Suite 400, Princeton, New Jersey.

3. Accord is a corporation organized and existing under the laws of the State of North Carolina, with its principal place of business at 1009 Slater Road, Suite 210B, Durham, North Carolina, 27703.

4. Actavis is a limited liability company organized and existing under the laws of the State of Delaware, with its principal place of business at Morris Corporate Center III, 400 Interpace Parkway, Parsippany, New Jersey.

B. The Invention

5. VELCADE® (bortezomib) for Injection is a proteasome inhibitor used in the treatment of patients with multiple myeloma and patients with mantle cell lymphoma who have received at least one prior therapy.

6. In 2003, the Food and Drug Administration ("FDA") granted "accelerated approval" to New Drug Application No. 21-602 for VELCADE® for Injection, for the treatment by intravenous administration of patients with multiple myeloma who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

7. VELCADE® for Injection was subsequently approved in 2005 for treatment by intravenous administration of patients with multiple myeloma who had received at least one prior therapy; in 2006 for treatment by intravenous administration of patients with mantle cell lymphoma who had failed at least one prior therapy; in 2008 for frontline treatment by intravenous administration of patients with multiple myeloma; in 2012 for subcutaneous administration; and in 2014 for treatment of adult patients with multiple myeloma who had previously responded to VELCADE® for Injection therapy and relapsed at least six months following completion of prior VELCADE® for Injection treatment.

8. The '446 patent has been listed in connection with VELCADE® for Injection in the FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations*, referred to as the "Orange Book."

[3] These facts are drawn primarily from the parties' jointly submitted statement of uncontested facts. (*See* D.I. 112-1.)

9. U.S. Patent No. 5,780,454 ("the '454 patent"), among others, is also listed in the Orange Book in connection with VELCADE® for Injection. The '454 patent, entitled "Boronic Ester and Acid Compounds," issued on July 14, 1998, is assigned to Millennium, and will expire on May 3, 2017. The '454 patent is prior art to the '446 patent and is of record in the prosecution of the '446 patent.[4]

10. Millennium sells VELCADE® for Injection in the United States.

C. The Patent-in-Suit

11. The '446 patent, entitled "Formulation of Boronic Acid Compounds," issued on March 30, 2004, naming Shanker Lal Gupta as the inventor. The '446 patent claims priority to Provisional Application No. 60/264,160, filed on January 25, 2001 ("the '160 provisional").

12. A Certificate of Correction issued for the '446 patent on September 6, 2005.

13. The '446 patent is assigned to the United States of America as Represented by the Secretary of Health and Human Services.

14. Millennium holds an exclusive worldwide license to the '446 patent for the research, development, and manufacture of Bortezomib for distribution, sale and use in oncology disease states. Pursuant to its license, Millennium has the right to bring suit for infringement and defend invalidity counterclaims in its own name and own behalf.

1. The Asserted Claims

15. Millennium asserts claims 20, 31, 49, and 53 ("Asserted Claims") of the '446 patent.

i. *'446 Patent, Claim 20*

16. Claim 20 of the '446 patent is directed to directed to lyophilized mannitol boronate ester compounds, including the lyophilized mannitol ester of bortezomib.

ii. *'446 Patent, Claim 31*

17. Claim 31 of the '446 patent is directed to preparing the lyophilized mannitol ester of bortezomib by lyophilizing a mixture of water, bortezomib and mannitol.

iii. *'446 Patent, Claim 49*

18. Claim 49 of the '446 patent is directed to a lyophilized cake comprising the lyophilized mannitol ester of bortezomib.

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[4] The parties agreed to refer to the '454 patent as the "Adams patent" because the number is similar to the patent-in-suit. Tr. 47.

iv. *'446 Patent, Claim 53*

19. Claim 53 of the '446 patent adds to the method of claim 31 the further step of reconstituting the lyophilized mixture comprising the mannitol ester of bortezomib with a pharmaceutically-acceptable carrier.

2. The Accused Products

i. *ANDAs Filed by the Defendants*

20. Millennium's VELCADE® for Injection is FDA-approved to treat multiple myeloma and mantle cell lymphoma. (D.I. 112-1, ¶¶ 11–13.)

21. Sandoz, Accord, and Actavis filed ANDA Nos. 203654, 204405, and 204332, respectively, seeking approval for the commercial manufacture, use, and sale of generic versions of VELCADE® for Injection. (*Id.*, ¶¶ 16, 20, 25.)

22. The defendants dispute that any of the asserted claims are valid. (*Id.*, ¶¶ 18, 23, 28.)

23. The defendants previously entered into stipulations regarding infringement of certain claims of the '446 patent including the Asserted Claims with the exception of Claim 53, which relies on induced infringement. (*See* D.I. 86, 92, 94.) The defendants challenge the alleged induced infringement of Claim 53. The primary issue presented at trial was obviousness.

D. Procedural History

24. In separately-captioned actions, Millennium filed complaints for patent infringement against Sandoz (C.A. 12-1011-GMS), Accord (12-490-GMS), and Actavis (12-1750-GMS) on August 2, 2012, November 19, 2012, and December 21, 2012, respectively.

25. Millennium's actions against Accord and Actavis were consolidated with the Sandoz action on April 23, 2013. (D.I. 21.)

III. FINDINGS OF FACT AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b). The court has considered whether the asserted claims are invalid due to obviousness and, if so, whether the defendants induced infringement of Claim 53 of the '446 patent. After having reviewed the entire record in this case, the parties' post-trial submissions, and the applicable law, the court concludes

that the asserted claims of the '446 patent are invalid due to obviousness.[5] The court will therefore grant the defendants' Rule 52(c) motion. The court's reasoning follows.

A. Obviousness

The defendants challenge the validity of each of the asserted claims as obvious in light of the prior art. The court finds, for the reasons that follow, that the defendants have established by clear and convincing evidence that the asserted claims of the '446 patent are obvious.

While worded differently, each claim has three central elements: (1) freeze-drying bortezomib, (2) using mannitol, (3) to form a bortezomib-mannitol ester.[6] Tr. 122–25 (Repta). Millennium asserts an invention date of December 1997 based on the first time that Dr. Valentino Stella freeze-dried bortezomib with mannitol.[7] Tr. 477 (Stella); PTX-32 at 13–17 (Waugh Notebook); Tr. 690–91 (Snow).

1. The Legal Standard

35 U.S.C. § 103(a) provides that 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 to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law that is predicated on several factual inquires. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Specifically, the trier of fact is directed to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but

[5] Accordingly, the court does not address Millennium's arguments of induced infringement of Claim 53. The court notes that the defendants' "good-faith belief of invalidity" is not a viable defense to induced infringement, had the court found the patents valid. *See Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920 (2015).

[6] In addition to the main three elements, Claim 53 adds the step of "reconstitution," which involves adding liquid to the freeze-dried cake to put the drug into solution for injection into the patient. DTX-1-012, cl. 53 ('446 patent); Tr. 111 (Repta).

[7] Dr. Stella and his assistant Wanda Waugh were added as inventors after an inventorship suit and decision in 2012. *See infra* notes 8, 10.

unsolved need, failure of others, acquiescence of others in the industry that the patent is valid, and unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A patent and each of its claims are presumed to be valid. 35 U.S.C. § 282(a). A party seeking to challenge the validity of a patent based on obviousness must demonstrate by "clear and convincing evidence" that the invention described in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. *Kao Corp. v. Unilever U.S., Inc.*, 441 F3d 963, 968 (Fed. Cir. 2006) (citation omitted). "Clear and convincing evidence is evidence that places in the fact finder 'an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" *Alza Corp v. Andrx Pharms., LLC*, 607 F. Supp. 2d 614, 631 (D. Del. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)). This burden of proof remains constant, even when a patent invalidity attack relies on the same prior art previously considered by the PTO. *See Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("The burden does not suddenly change to something higher—'extremely clear and convincing evidence' or 'crystal clear and convincing evidence'—simply because the prior art references were considered by the PTO.") Practically speaking, however, "it may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered." *Id.*

Importantly, in determining what would have been obvious to one of ordinary skill in the art, the use of hindsight is not permitted. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007) (cautioning the trier of fact against "the distortion caused by hindsight bias" and "arguments reliant upon ex post reasoning" in determining obviousness). In *KSR*, the Supreme Court rejected the rigid application of the principle that there should be an explicit "teaching, suggestion, or motivation" in the prior art, the nature of the problem, or the knowledge of a

person having ordinary skill in the art, in order to find obviousness. *See KSR*, 550 U.S. at 415. The *KSR* Court acknowledged, however, the importance of identifying "'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." *Takeda Chem. Indus. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1356–57 (Fed. Cir. 2007) (quoting *KSR*, 550 U.S. at 418).

"Obviousness does not require absolute predictability of success" but, rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolado, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988)). To this end, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Moreover, while the Federal Circuit has noted that pharmaceuticals can be an "unpredictable art," to the extent that results may be unexpected, it also has recognized that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives "might support an inference of obviousness." *See Eisai Co. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). Obviousness does not require proof that something is "the *best* option, only that it be a *suitable* option from which the prior art did not teach away." *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014).

2. The Level of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") of the '446 patent would have had a graduate or undergraduate degree in pharmaceutical sciences or a related field and at least two years' experience formulating pharmaceutical products.[8]

[8] The court's definition is drawn from the testimony of Dr. Arnold Repta. Tr. 104–05. While Dr. Repta's definition was slightly different than that of Dr. Bradley Anderson and Dr. Roger Snow, all doctors testified that their opinions on obviousness would not change, regardless of whose definition of a POSA applied. *See* Tr. 106, 624, 705. The court concludes that the parties' definitions of a POSA do not differ in any meaningful way.

3. The Scope and Content of the Prior Art and Differences Between the Claimed Subject Matter and the Prior Art

As a preliminary matter, Millennium asserts that the defendants "improperly rely on a host of prior art references without identifying any specific combination (or single reference) that purportedly renders the claims of the '446 obvious." (D.I. 132, ¶ 3.)

The defendants argue that the asserted claims are obvious because the '446 patent claims the inherent result of an obvious process—namely, that freeze-drying bortezomib with mannitol produces an ester. (D.I. 133, ¶ 2.) Millennium argues that the defendants failed to prove that a POSA would have been motivated to modify bortezomib to make the lyophilized mannitol ester. (D.I. 132, ¶ 114.)

a. *Specific Combination of References*

Millennium argues as a preliminary matter that the defendants' expert, Dr. Arnold Repta, "did not identify any specific combination of references or any single reference that supposedly renders the asserted claims obvious, but instead cited 17 references to support his obviousness opinion." (*Id.*, ¶ 48.)

A party asserting a patent is invalid for obviousness must prove that one skilled in the art would have been motivated to combine the claimed references. *See Braintree Labs., Inc. v. Novel Labs. Inc.*, 749 F.3d 1349, 1359 (Fed. Cir. 2014). There must be a "plausible rational[e] as to why the prior art references would have worked together." *Power-One, Inc. v. Artesyn Techs., Inc.*, 599 F.3d 1343, 1352 (Fed. Cir. 2010).

The court concludes that Dr. Repta's opinion provides appropriate reasoning to support his determination that the '446 patent is invalid for obviousness. As discussed more fully below, Dr. Repta properly conducted his obviousness inquiry and addressed how a POSA would have found the claims obvious based on the art described. Unlike the concerns articulated by the Court in

Braintree, Dr. Repta's utilization of the references supports a "plausible rationale" as to why the prior art references would have worked together and, further, clearly articulates how and why a POSA would have been motivated to lyophilize bortezomib with mannitol to form an ester. *See* Tr. 196.

b. *Bortezomib is The Closest Prior Art*

The Adams, or '454, patent provides the sole prior art for the Bortezomib compound. There is no dispute that it qualifies as relevant prior art.

Millennium's predecessor, ProScript, first applied for a patent on bortezomib in 1995. DTX-20. The Adams patent disclosed that bortezomib was a potent anti-cancer drug. Tr. 869 (Anderson). As Millennium's expert Dr. Anderson acknowledged, the Adams patent identified bortezomib as a "very potent, promising lead candidate" with the "highest *in-vivo* activity" of all the compounds disclosed in the patent. Tr. 869, 743. The Adams patent not only discloses bortezomib, but also esters of bortezomib. Claim 18 expressly claims "pharmaceutically acceptable salts and esters" of bortezomib. '454 patent, 65:19–21; Tr. 865 (Anderson). The Adams patent further claimed "pharmaceutical compositions" of the claimed esters, including the bortezomib esters. '454 patent, 65:22–35, 66:28–30; Tr. 875–76, 873 (Anderson). The Adams patent discloses and claims the use of "prodrugs." Tr. 876–77. A "prodrug"—like the claimed mannitol ester of bortezomib—is a drug compound "that . . . upon administration rapidly releases the active agent." Tr. 256 (Repta); *see also* Tr. 256 (Repta); Tr. 766 (Anderson).

c. *Decision to Lyophilize Bortezomib Was Obvious*

Millennium asserts that in light of the prior art a person of ordinary skill would avoid lyophilization in attempting to develop a formulation involving boronic acid compounds. (D.I. 132, ¶¶ 68–69.)

According to both parties' experts, lyophilizing (or freeze-drying) is one of the "top two" choices a formulator would consider. Tr. 819–20 (Anderson); Tr. 97–98 (Repta). After ProScript ran into issues developing a liquid formulation that would provide the long-term shelf life needed for commercialization, Proscript partnered with the National Cancer Institute ("NCI") to develop a formulation. Tr. 614 (Adams). NCI, in turn, worked with contract formulators at the University of Kansas ("KU") including Dr. Stella and his assistant Wanda Waugh. Dr. Stella testified that he initially attempted a liquid formulation. Tr. 457, 510–11 (Stella). Dr. Stella's solution work was not immediately successful. Tr. 513 (Stella). He next attempted a freeze-dried formulation because as he explained "[h]e would be remiss if [he] didn't try [freeze-drying]" after encountering stability problems with a solution. Tr. 511 (Stella).

The defendants' expert, Dr. Repta, testified to three primary references that establish lyophilization as a standard formulation option. Tr. 129–31. Tr. 114-17 (Repta); DTX-207-011 (Repta 1981); DTX-728-045 (Pharm. Dosage Forms 1992); DTX-556-004 (Remington's 1990). While a liquid formulation is preferable to a lyophilized formulation, the prior art clearly established that lyophilized formulations were considered a viable second choice. (*See* DTX-556-004 "[d]espite both the high initial capital equipment costs and the high running costs of the method, lyophilization has become the most important method for the stabilization of labile pharmaceutical products with limited shelf lives in dilute solution."). The court agrees that one skilled in the art would have considered these references in attempting to stabilize bortezomib.

Millennium asserts that "lyophilization would not necessarily address the instability of bortezomib" because bortezomib was known to be unstable even in the dry state as a freestanding solid compound. (D.I. 132, ¶ 77.) Millennium's expert witness, Dr. Anderson, relied on the Snyder reference to support his opinion that lyophilization may not improve stability of a boronic

acid compound. Tr. 750–51. On cross-examination, however, Dr. Anderson conceded that the Adams patent discloses the use of lyophilization in a number of examples. Tr. 818–19. Further, Dr. Anderson agreed that a formulator working with investigational anti-cancer drugs seeking to develop an intravenous formulation would look to either a ready-to-use liquid solution or freeze-drying. *Id.*

The court finds that the testimony of Dr. Repta is persuasive and supported by the evidence. As of the priority date lyophilization was well-known in the field of formulation and often utilized when a liquid formulation provided limited success.[9] Dr. Repta credibly testified and the prior art establishes that lyophilization had been used for decades, and a POSA at least would have considered the technique in developing stable formulations. Dr. Anderson's expert opinion did not disprove the defendants' position that freeze-drying was considered by those skilled in the art to reliably improve stability by eliminating the three main sources of instability in solutions: molecule movement, hydrolysis, and oxidation. Once a liquid formulation proved unsuccessful; the obvious next step was to attempt lyophilization. As Dr. Stella noted as early as 1992, "[i]f a drug is unstable in aqueous solution, generally a freeze-dried formulation must be developed." Tr. 512 (Stella); DTX-742-005 (1992 Stella Ltr.). The court concludes that the decision to attempt a lyophilized formulation of bortezomib was "[t]he routine application of a

[9] This determination is supported by the positions Millennium took during the inventorship suit and arbitration against Dr. Stella and his assistant Wanda Waugh. Specifically, Millennium and NCI argued that there "was nothing inventive about thinking to lyophilize bortezomib." DTX-78-038 (Mill. Arb. Br.). Millennium and NCI said it was "an expected step under the NCI contract, and it required the exercise of only ordinary skill in the art," and it was "not a significant or inventive contribution." DTX-261-041-42 (2012 Mill. Arb. Br.). They further argued that "[a]ll of [Dr. Stella and Ms. Waugh]'s alleged contributions can be dismissed on the ground that they constituted no more than routine steps based on the exercise of routine skill; indeed, they were natural and expected formulation options under the contract." DTX-78-038 (Mill. Arb. Br.). Although inventorship and obviousness inquiries are not identical, Millennium's prior statements appear to confirm that lyophilization was a known and common technique in the field.

well-known problem-solving strategy" and that of "a skilled artisan, not of an inventor." *See Pfizer*, 480 F.3d at 1368 (internal citations omitted).

d. *Decision to Lyophilize Bortezomib with Mannitol was not Inventive*

Dr. B. Rao Vishnuvajjala from the NCI first "suggested using mannitol" to his subordinate, inventor Dr. Shanker Gupta. Tr. 81–82 (Vishnuvajjala). He made that suggestion because he "expected that lyophilizing [bortezomib] with mannitol would solve the degradation issue" and thus "address the stability issue" with the formulation. Tr. 82 (Vishnuvajjala). On October 6, 1997, Dr. Gupta sent an email to Dr. Stella suggesting four bulking agents for freeze-drying, including mannitol, as an "added insurance" policy if the solution work was not successful. DTX-17-001 (1997 Gupta Email). Far from suggesting that he was offering anything inventive, Dr. Gupta simply provided a "disparate list of bulking agents" (*id.*), which he expected to work based on "[his] experience and knowledge of lyophilization." Tr. 318. The KU scientists started their work on a freeze-dried formulation in "late November" of 1997 (Tr. 516 (Stella)), and succeeded within weeks, with "the first batch [they] made" with mannitol. Tr. 475–76 (Stella); PTX-37 at 9 (Dec. 1997 Report). Dr. Stella conceded at trial that Mannitol was an "obvious option" as the "most popular" bulking agent, and simply "not innovative" to "suggest using mannitol to freeze-dry bortezomib." Tr. 516, 518, 522–23.

Even Dr. Anderson conceded that a skilled formulator would immediately "consider" using mannitol (Tr. 800), which was "highly popular." Tr. 848–49. Dr. Repta explained that it was so popular because "you [can] administer it by intravenous route"; it also "has no pharmacological effects," is "very water-soluble," and "forms really nice cakes" that "dissolve rapidly and . . . are robust." Tr. 147, 313; *see also* DTX-738-003 (1994 Handbook); DTX-205-001 (Kim 1998); DTX-529-075 (Bashir 1973). He could not "remember using . . . anything other

than mannitol as a bulking agent in the numerous formulations [KU] made through lyophilization." Tr. 146–47.

The Adams patent also pointed directly to mannitol. It taught that freeze-drying was appropriate for the claimed acids and esters, by including four different freeze-drying examples. '454 patent at Examples 3.B, 4.B, 8.D, 13.K; Tr. 815–16 (Anderson). Dr. Anderson acknowledged nothing in the patent taught "that bortezomib would be any less appropriate for lyophilization" than compounds in the examples. Tr. 817. The Adams patent explained that scientists should make esters using "preferably, a dihydroxy compound." Tr. 807 (Anderson); see '454 patent at 10:12–16. Mannitol is a dihydroxy compound. Tr. 161 (Repta); Tr. 321 (Gupta); Tr. 508 (Stella); Tr. 600 (Adams); Tr. 672 (Snow); Tr. 807 (Anderson). Dr. Anderson argued that there are "millions" of "dihydroxy compounds" capable of forming bortezomib esters. Tr. 744, 807-08.[10] But Dr. Repta's explanation that only "half a dozen or so" are "pharmaceutically acceptable bulking agents" -- the "most prominent" of which is "mannitol" -- is highly convincing. Tr. 164.

The court concludes that mannitol was among the "finite number of identified, predictable solutions" to freeze-drying investigational anti-cancer drugs like bortezomib. *KSR*, 550 U.S. 421. It was a "suitable option from which the prior art did not teach away." *See Par*, 2014 WL 6782649, at *9. The choice was an obvious one. In reviewing the prior art, the court finds that one skilled in the art would have found it obvious to choose mannitol and would have had a reasonable probability of success in light of the prior art.[11]

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[10] Dr. Anderson's opinion here is similar to an analogous opinion he offered in *Pfizer*, where he argued that there were an "unlimited" number of salt options when in fact there were only 53 FDA approved salts—an opinion the Federal Circuit said "a reasonable fact-finder could not accept" in view of the FDA limitations imposed on pharmaceutical products. 480 F.3d at 1362.

[11] Again, the court finds the earlier positions of the now named inventors persuasive support for the proposition that lyophilizing with mannitol was an obvious formulation decision to a POSA. *See supra* note 8. Specifically, KU—which gets royalties under the '446 patent—acknowledged that choosing mannitol to freeze-dry

e. *It Would Have Been Obvious to a POSA that Freeze-Drying Bortezomib with Mannitol Would Produce A Bortezomib-Mannitol Ester*

Millennium asserts that even if a POSA were inclined to experiment with lyophilization to form an ester, "they would understand that formation of the ester would not be inevitable, and could vary widely depending on the particular conditions used, including concentration, ratios of ingredients, and temperature." (D.I. 132, ¶ 90.) Further, Millennium asserts that none of the references cited by Dr. Repta concerning boron compounds teaches the use of boronate esters to improve the stability of a boronic acid compound by preventing oxidation. (*Id.*, ¶ 60.) Millennium points out that the references cited by Dr. Repta teach not only that boron compounds may form new compounds with dihydroxy compounds under the right conditions but also that the properties of these compounds are unpredictable. (*Id.*, ¶¶ 63–64.) Millennium argues that a POSA formulating bortezomib would avoid forming an ester because the prior art makes clear that the rate and extent of ester formulation and dissociation is unpredictable. (*Id.*)

The defendants contend that if the court finds obvious the first two steps—freeze-drying bortezomib with mannitol—the patent is necessarily invalid because ester formation is the inherent result of that combination. "[I]nherency may supply a missing claim limitation in an obviousness analysis." *Par*, 2014 WL 6782649, at *6. An element is inherent "when the limitation at issue is the 'natural result' of the combination of prior art elements." *Id.* at *7. Dr. Repta explained, mixing bortezomib and mannitol will "inevitabl[y]" form the ester.

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bortezomib was obvious: "the idea to try mannitol was natural and expected of those of ordinary skill in the art." DTX-255-067 (KU Arb. Br.). In 2010, in preparation for a deposition in the royalty dispute, Dr. Adams conducted an "investigation" about whether Dr. Stella had made an "inventive contribution." Tr. 591 (Adams). Based on that investigation, Dr. Adams "concluded that [he] had no facts, no evidence, that Dr. Stella had made an inventive contribution." Tr. 591–92 (Adams). He came to this conclusion even though he knew that Dr. Stella had "freeze-dried bortezomib with mannitol" and "that procedure produced a bortezomib-mannitol ester." Tr. 591–93 (Adams).

Similarly, seven days before Millennium filed its priority application, Millennium's lead formulator called the claimed freeze-dried formulation an "obvious option" while noting that "one of the most commonly used excipients for a lyophilized formula is mannitol." DTX-144-001 (2001 Lai Email); *see* Tr. 348–50 (McCubbin).

The defendants also assert that Millennium admitted inherency by excluding Dr. Adams as an inventor even though he was the first to identify the ester formation in October 1998 and asserting an invention date in December 1997 when Dr. Stella made the claimed formulation. (D.I. 133, 148.) The defendants point to Dr. Anderson's acknowledgment that the named inventors "didn't have any idea that bortezomib had formed an ester with mannitol" before Dr. Adams' realization, and "there is no evidence that they had the invention in mind" before September 1998. Tr. 865. Similarly, Dr. Gupta "did not know at that point in time whether an ester had been formed . . . ." Tr. 320. Millennium's 30(b)(6) witness, Dr. Quentin McCubbin, affirmed "it wasn't Dr. Gupta who had the idea ... that [they] were forming an ester"; "[t]here's no evidence that [Dr. Stella] had thought about an ester formation"; and Ms. Waugh "didn't know anything about the ester." Tr. 342. In fact, Dr. Stella admitted that he "didn't learn that the ester had formed" until "around 2005," "when [he] read the ['446] patent." Tr. 532–33. The defendants argue that by omitting Dr. Adams from its patent application and claiming an invention date of December 1997, Millennium conceded as a matter of law that the ester is the "natural result" of freeze-drying bortezomib with mannitol. (D.I. 132, ¶ 150 (quoting *Par*, 2014 WL 6782649, at *7). The court agrees and concludes that the inventors were not required to recognize the ester as of December 1997 because it is an "inherent propert[y]" that falls under the "rare exception[] to the rule" that "every limitation" of a claim "must have been known to the inventor at the time of the alleged conception." *Hitzeman v. Rutter*, 243 F.3d 1345, 1354–55 (Fed. Cir. 2001).

f. *The Adams Patent Provided a POSA the Motivation to Combine*

Millennium cannot claim that the prior art teaches against what its own prior art patent affirmatively claims. Millennium's patent—the Adams patent—specifically teaches that formulators "can use" the claimed "esters as pharmaceutical compositions." Tr. 607:13-16

(Adams). The patent also specifically claims "pharmaceutical compositions" of bortezomib "esters" to be used as "prodrugs," including the mannitol ester. '454 patent 65:19–21, 66:28–30; Tr. 870, 874, 875–77, 880 (Anderson). Second, as Dr. Repta explained, skilled formulators would be motivated to create a mannitol ester to improve bortezomib's stability and solubility. Tr. 169. Millennium's 30(b)(6) witness agreed, saying that the "first thing to do to stabilize [boronic acids like bortezomib] would be to form an ester." Tr. 335 (McCubbin). And while he emphasized there were no guarantees, Dr. Anderson similarly conceded that "ester formation can dramatically increase the solubility of a compound," "especially" when the ester is formed with a "highly soluble" "molecule like mannitol." Tr. 847. Third, as Dr. Anderson conceded, ester formation is "generally" "not a problem" because when you "put an ester in water . . . you expect it to hydrolyze" (Tr. 836), meaning the ester breaks apart, thus freeing the active ingredient to achieve its biological activity in the body. Tr. 867. Dr. Repta shared this view (Tr. 152-53, 304-05), as did Dr. McCubbin. Tr. 350–51. That is precisely what the Adams patent claimed and taught happens with the claimed esters. Tr. 870–73 (Anderson). For the reasons stated above, the court concludes that the defendants have established a *prima facie* case that the '446 patent was obvious in light of the prior art.

4. Secondary Considerations

The final factor in assessing obviousness is evaluating the objective indicia of non-obviousness, often referred to as secondary considerations. Millennium argues that the relevant considerations in this case are unexpected results, commercial success, and long-felt but unmet need.

"Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Pfizer*, 480 F.3d at 1372. A strong case of prima facie

obviousness . . . cannot be overcome by a far weaker showing of objective indicia of nonobviousness. *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371. Moreover, "[a] nexus between the merits of the claimed invention and evidence of secondary considerations is required in order for the evidence to be given substantial weight in an obviousness decision." *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327 (Fed. Cir. 2008) (alteration in original) (quoting *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed. Cir. 2000)). In other words, the secondary considerations must be commensurate in scope—"coextensive"—with the claimed features of the invention. *Id.*; *see also MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264–65 (Fed. Cir. 2013).

a. Unexpected Results

Millennium asserts that a person of ordinary skill would not have expected a lyophilized mannitol ester of bortezomib to provide these dramatic improvements in stability, solubility and dissolution as compared to bortezomib. (D.I. 132, ¶ 100.) Millennium failed to present any credible evidence at trial about what a skilled artisan would have expected. *See Bristol-Myers*, 752 F.3d at 977 ("[E]vidence of unexpected results must establish . . . that the difference would not have been expected by one of ordinary skill in the art at the time of the invention."). Millennium's experts testified that they did not know whether the bortezomib-mannitol ester was more stable or soluble than the closest prior art bortezomib glycerol ester. Tr. 890-91 (Anderson); Tr. 684 (Snow). Millennium also failed to establish any difference between the claimed invention and the closest prior art. *See Bristol Myers*, 752 F.3d at 977 ("[E]vidence of unexpected results must establish that there is a difference between the results obtained [through the claimed invention] and those of the closest prior art[.]"). Millennium's experts compared the bortezomib-

mannitol ester to examples that did not contain esters. The court agrees with the defendants that the closest prior art were the bortezomib esters disclosed in the Adams patent.

b. Commercial Success and Long-Felt Need

Commercial success is an indication of nonobviousness "because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). When commercial success has been demonstrated and "the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention." *J.T. Eaton & Co. v. Atl. Paste & Glue Co*, 106 F.3d 1563, 1571 (Fed. Cir. 1997); *see also Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1394 (Fed. Cir. 1988) ("It is sufficient to show that the commercial success was of the patented invention itself.").

Millennium's commercial success and long-felt need arguments focus on the fact that "[t]he bortezomib compound alone cannot be administered to patients, and therefore required a pharmaceutical formulation." (D.I. 132, ¶ 35.) Here, the Adams patent precluded alternative inventions from competing in the market. The evidence at trial established that a number of other formulations provided a viable route to commercial production but were disregarded on economic rather than efficacy grounds. No persuasive evidence was provided to show any advantage attributable to the claimed formulation over the other potential formulations available to Millennium. For substantially the same reasons, Millennium was similarly unsuccessful in presenting persuasive evidence of a long-felt need. While the success of bortezomib in treating multiple myeloma cannot be understated, the lyophilized mannitol ester of bortezomib did not

solve any problem having "persisted over a long period of time without resolution by the prior art . . . ." *Hitachi Koki Co. v. Doll*, 620 F. Supp. 2d 4, 30 (D.D.C. 2009).

Based on the evidence presented at trial, the court concludes that Millennium's assertions do not undermine its obviousness finding.

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In sum, the defendants have presented a *prima facie* case by clear and convincing evidence that the asserted claims of the patents-in-suit are invalid as obvious. Moreover, the court finds that the secondary, objective indicia do not overcome the finding of obviousness. The defendants have shown by clear and convincing evidence that the '446 patent is obvious and therefore invalid under 35 U.S.C. § 103.

IV. CONCLUSION

For the reasons stated above, the court concludes that: (1) the asserted claims of the '446 are invalid due to obviousness. (2) The defendants' Rule 52(c) motion (D.I. 133) is granted. (3) Millennium's Rule 52(c) motion (D.I. 132) is denied.

Dated: August 20, 2015

UNITED STATES DISTRICT JUDGE