IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK SHARP & DOHME CORP.,

Plaintiff,

v.

HOSPIRA INC.,

Defendant.

Civil Action No. 14-915-RGA

TRIAL OPINION

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October 7, 2016

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiff brought this patent infringement suit against Defendant on July 11, 2014. (D.I. 1). On May 29, 2014, Defendant informed Plaintiff that it had filed an ANDA, seeking approval to engage in the commercial manufacture, use, or sale of generic versions of Plaintiff's Invanz product. (D.I. 191, Ex. 1 ¶ 15). Plaintiff alleges that this ANDA filing infringes U.S. Patent Nos. 5,952,323 ("the '323 patent") and 6,486,150 ("the '150 patent") (collectively, "the patents-in-suit").

The patents-in-suit, and Plaintiff's Invanz product, relate to an antibiotic called ertapenem. Ertapenem is a member of a class of antibiotics called carbapenems. Ertapenem is administered by intravenous, subcutaneous, or intramuscular injection. Ertapenem is highly unstable. (Tr. 760:5-13).[1] Specifically, ertapenem may undergo two types of degradation reactions that are relevant to this case: hydrolysis and polymerization. (Tr. 761:1-3, 856:7-13).

Hydrolysis, specifically "ring-opening hydrolysis," is a problem for all compounds which, like ertapenem, have a beta-lactam ring. (Tr. 88:11-18). Hydrolysis occurs when water breaks open the beta-lactam ring, thereby rendering the molecule ineffective. (Tr. 397:19-398:8, 765:21-24, 855:18-856:13). While beta-lactams may undergo hydrolysis at any pH, hydrolysis occurs more readily as pH values move away from neutral—i.e., as the solution becomes increasingly basic or acidic. (Tr. 89:2-19, 90:13-17, 397:21-398:20, 761:22-762:2, 924:7-17).

Polymerization occurs when two or more molecules of the same type react with each other to form what is called a polymer. Dimerization is polymerization when only two molecules are involved. The resulting molecule is called a "dimer." (Tr. 761:13-16). When dimerization occurs, the original molecules have been fundamentally changed. (Tr. 765:21-

[1] References to the trial transcript are identified as "Tr." The trial transcript is filed on the docket at D.I. 212 to D.I. 215.

766:5). Dimerization of ertapenem occurs when the pyrollidine amine of one ertapenem molecule reacts with the beta-lactam ring of another ertapenem molecule to form a dimer. (Tr. 855:1-3).

Ertapenem was first claimed in U.S. Patent No. 5,478,820 ("the '820 patent"), which is not asserted here. Rather, this case concerns the '323 and the '150 patents. The asserted claims of the '323 patent[2] are directed to a stable pharmaceutical composition containing ertapenem, and to a method of stabilizing ertapenem. (PTX 1 at 9:14-28, 10:31-64).

The '323 patent teaches that by increasing the pH of the ertapenem compound—through the addition of carbonate or bicarbonate—the hydrolysis reaction that tends to occur at low pH ranges can be avoided. While elevating the pH may increase the likelihood that polymerization occurs (Tr. 817:2-16), the '323 patent explains that this polymerization reaction can be prevented through the formation of a carbamate adduct ("the adduct").[3] (Tr. 806:19-807:20). The adduct is formed when ertapenem reacts with a carbon dioxide source—in this case, carbonate or bicarbonate—at a pH range of about 6.0 to 9.0. (Tr. 762:19-763:3). When the carbamate adduct forms, at ertapenem's pyrollidine ring, the pyrollidine nitrogen is no longer reactive, and therefore cannot react with the beta-lactam ring, thereby preventing the polymerization reaction. (Tr. 91:8-18, 762:11-18).

The asserted claims of the '150 patent[4] are directed to "[a] process for preparing a final formulation product of formula Ia, . . . or its pharmaceutically acceptable salt." (PTX 2 at 18:11-23). Formula Ia is a generic chemical structure which encompasses the carbamate adduct of ertapenem and other related carbapenem molecules. (Tr. 113:9-19, 119:5-11).

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[2] Plaintiff asserts independent claims 2 and 4 and dependent claims 5 and 6.

[3] The carbamate adduct is a particular form of ertapenem. In this opinion, the adduct may be referred to as the adduct, the carbamate adduct, or the carbon dioxide adduct.

[4] Plaintiff asserts independent claim 21 and dependent claims 22-34.

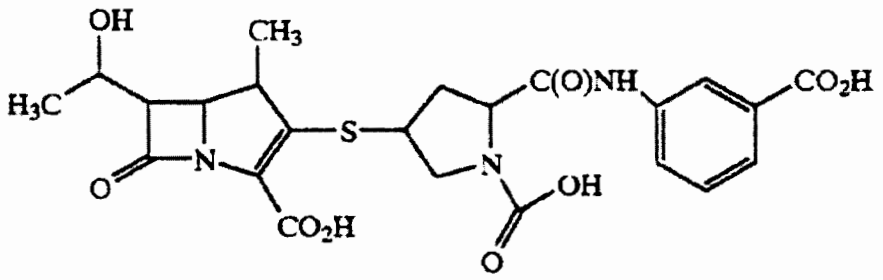
The Court held a bench trial on April 18-21, 2016. Defendant concedes that its generic product would infringe claims 2 and 4-6 of the '323 patent, if those claims are not held invalid or unenforceable. (D.I. 191, Ex 1 ¶ 18). Defendant argues that all of the asserted claims of the '323 patent are invalid as obvious and anticipated, and that asserted claims 4-6 are invalid for lack of written description. Defendant contests infringement as to the '150 patent, and asserts that it is invalid on grounds of anticipation and obviousness.

I. '323 PATENT

Independent claim 2 of the '323 patent reads:

> A pharmaceutical composition which is comprised of a compound represented by formula II:

II

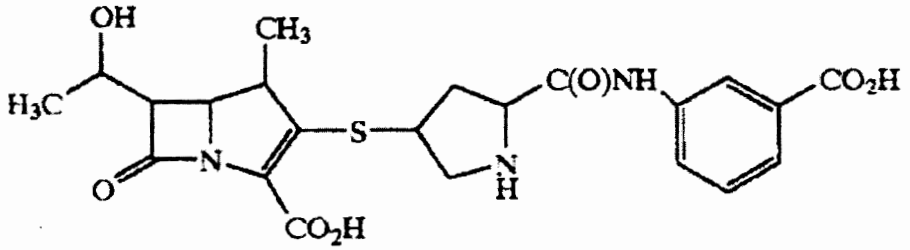


> or a pharmaceutically acceptable salt, prodrug or hydrate thereof, in combination with a pharmaceutically acceptable carrier.

(PTX 1 at 9:14-28). Independent claim 4 reads:

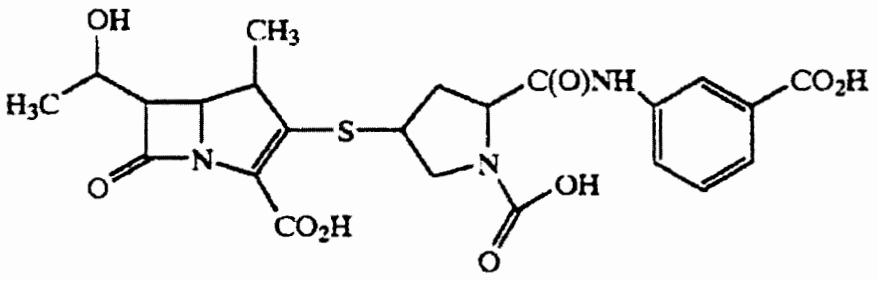
> A method of stabilizing a carbapenem of the formula I:

I



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, comprising adding to the compound a sufficient amount of a carbon dioxide source to form a compound of formula II:

II



or a pharmaceutically acceptable salt, prodrug or hydrate thereof.

(*Id.* at 10:30-57). Dependent claim 5 limits the carbon dioxide source to "carbon dioxide, sodium carbonate and sodium bicarbonate," while dependent claim 6 further limits the carbon dioxide source to "sodium carbonate and sodium bicarbonate." (*Id.* 10:58-64).

A. Anticipation

i. Legal Standard

A patent claim is invalid as anticipated under 35 U.S.C. § 102 if "within the four corners of a single, prior art document . . . every element of the claimed invention [is described], either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Callaway Golf Co. v. Acushnet Co.*, 576 F.3d 1331, 1346 (Fed. Cir. 2009) (alterations in original). "Thus, a prior art reference without express reference to a claim limitation may nonetheless anticipate by inherency." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005). To establish inherency, "prior art [must] necessarily function[] in accordance with, or include[], the claimed limitations." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). In other words, "[i]nherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trinitec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295

(Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). Inherent anticipation does not, however, "require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure." *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). "[T]he party asserting invalidity due to anticipation must prove anticipation, a question of fact, by clear and convincing evidence." *Orion IP, LLC v. Hyundai Motor Am.*, 605 F.3d 967, 975 (Fed. Cir. 2010).

ii. Findings of Fact

1. The level of ordinary skill in the art is a scientist responsible for drug formulation, such as a pharmaceutical chemist, physical chemist, medicinal chemist, or organic chemist, involved in the research and development of pharmaceutical compounds. The person of ordinary skill would have either: (1) a Ph.D., in a field related to pharmaceutical formulation and processing (such as pharmaceutical science, pharmacy, physical chemistry, organic chemistry, or pharmaceutics) and at least three years of experience in pharmaceutical compound development; or (2) a similar master's degree and at least five years experience in pharmaceutical compound development. Such an individual would also be familiar with or have access to the pertinent scientific literature.

2. The '820 patent is prior art.

3. The pH of the monosodium salt of ertapenem is about 5.5.

4. The '820 patent does not disclose the pH conditions required for the formation of the adduct.

5. The adduct would not necessarily form under the conditions described by the '820 patent.

6. The '820 patent does not anticipate the asserted claims of the '323 patent.

iii. Conclusions of Law

Defendant contends that the asserted claims of the '323 patent are inherently anticipated by the '820 patent. Specifically, Defendant contends that, although the '820 patent does not expressly disclose the carbamate adduct, the adduct will "'necessarily form' under the conditions taught by the '820 patent." (D.I. 211 at p. 6) (quoting Tr. 610:17-24). In other words, if one simply follows the steps of the '820 patent, the adduct will "just happen[]." (*Id.*) (quoting Tr. 884:18-885:6). I find otherwise. The '820 patent does not teach the key pH conditions for the formation of the adduct. Thus, while it is possible that the teachings of the '820 patent would result in the formation of the adduct, Defendant has not shown that the adduct will necessarily result.

The '323 patent states that the adduct does not form outside the pH range of "about 6.0 to about 9.0." (PTX 1 at 2:16-17). The '820 patent does not explicitly disclose this pH range, or, indeed, any other pH range. (Tr. 609:2-16). Defendant argues that a person of ordinary skill in the art,[5] reading the '820 patent, would recognize that it describes mixing a "sufficient amount of alkali carbonate or bicarbonate with ertapenem and at appropriate pH," such that the adduct will form. (Tr. 618:5-18).[6]

Defendant's argument hinges on the assertion that a person of skill in the art, when formulating ertapenem in accordance with the teachings of the '820 patent, would seek to obtain

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[5] The parties agree that a person of ordinary skill in the art is "a scientist responsible for drug formulation, such as a pharmaceutical chemist, physical chemist, medicinal chemist or organic chemist, involved in the research and development of pharmaceutical compounds." (D.I. 191, Ex. 1 at 5-6). The person of ordinary skill has either "a Ph.D., in a field related to pharmaceutical formulation and processing . . . and at least three years of experience in pharmaceutical compound development; or . . . a similar master's degree and at least five years experience in pharmaceutical compound development." (*Id.* at 6). "Such an individual would also be familiar with or have access to the pertinent scientific literature." (*Id.*).

[6] The '820 patent teaches that "an acidic compound of the present invention may be dry blended with an alkali metal carbonate or bicarbonate." (DTX 19 at 7:13-15).

a pH in the 6.0 to 9.0 range described in the '323 patent. In support of its anticipation defense, Defendant relies on its expert, Dr. Timko. Dr. Timko begins his analysis by noting that the '820 patent teaches that ertapenem could be mixed with alkali carbonate or bicarbonate. (DTX 19 at 7:10-14; Tr. 601:2-13). Dr. Timko opines that the "purpose" of this mixture "would be to obtain approximately a seven pH."[7] (Tr. 606:13-20). This pH would be ideal, Dr. Timko contends, because it "would get a suitably stable dosage form." (Tr. 606:13-20; *see also* Tr. 609:9-16, 610:6-16). Additionally, Dr. Timko notes that the '820 patent also explains that "[a] preferred pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection." (DTX 19 at 7:40-43; Tr. 602:13-21). Dr. Timko contends this is important because intravenous injection at a pH other than neutral would be painful. (Tr. 608:5-14). Thus, Defendant maintains that a skilled artisan, reading the '820 patent, would seek "to obtain a suitable, appropriate intravenous, intramuscular, subcutaneous formulation . . . [by] mix[ing] sufficient bicarbonate or carbonate with the drug to a neutral pH to obtain a suitable product." (Tr. 610:6-16).

Dr. Timko's conclusion—that a person of ordinary skill would raise pH to optimize stability—finds little support in the evidence introduced at trial. Dr. Timko, rather than

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[7] Ertapenem is polyionizable. (Tr. 781:9-24). There are four different ionic forms of it: the EH3 plus form (also, "fully protonated"), the "EH2 plus-minus" form, (also, "zwitterion"), the "EH minus" form (also, "monoanion" or "monosodium salt"), and the "dianion" form (also, "basic"). (Tr. 751:18-752:19, 801:15-804:6). In each of the first three forms, all of which are acidic, the pyrollidine group is fully charged. (Tr. 803:1-8, 808:18-809:1). When the pyrollidine group is charged, ertapenem cannot undergo polymerization, and it cannot react with a carbon dioxide source to form the adduct. (Tr. 803:9-11). Thus, only the dianion form can undergo polymerization or form the adduct. (Tr. 803:19-804:1, 806:19-807:5). At very low pH levels, ertapenem would likely exist only in the EH3 plus form, its most acidic form. (Tr. 801:22-802:8). As pH increases, ertapenem will exist in both the fully protonated and zwitterion form. (Tr. 802:11-16). As pH continues to increase, the fully protonated form will begin to disappear, and the monoanion form will begin to appear. (Tr. 802:18-23). The pH of the monosodium salt of ertapenem, the form upon which most of Plaintiff's anticipation theory is based, is about 5.5. (Tr. 425:18-24, 870:7-10, 886:20-23). When the pH is raised to about 6, the dianion form begins to appear. (Tr. 805:16-22).

explaining why an ordinary-skilled artisan would choose a neutral pH in a formulation, or how the '820 patent teaches that, relies on vague assertions. "[M]y education, my experience basically tell me that, you know, this is where you would want to be if you are going to be formulating the drug . . . . – you would want to optimize the stability, and you would want to optimize the pH." (Tr. 609:9-16; *see also* Tr. 606:13-20, 608:15-609:7).

Plaintiff's expert, Dr. Stella, provides several reasons why a person of ordinary skill in the art, reading the '820 patent, would not have formulated ertapenem at a neutral pH. Rather, Dr. Stella opines, a person of ordinary skill would have at least three good reasons to formulate ertapenem at a pH below 6.0. First, most hydrolytically unstable drugs, such as beta-lactams,[8] experience "maximum stability in the pH range of about 3.5 to 5." (Tr. 771:1-3, 797:21-798:1). Second, in the cases of thienamycin and ampicillin, two other beta-lactams, polymerization reaches optimal levels around pH values of 7 to 7.5. (Tr. 769:9-770:21). Thus, at neutral pH, a person of ordinary skill in the art would expect ertapenem to undergo polymerization, which would destroy the formulation. (Tr. 798:2-9). Third, meropenem, a structurally similar compound,[9] is most stable in solution at a pH between 5 and 6. (Tr. 786:11-787:10; PTX 409).[10]

Accordingly, a person of ordinary skill in the art would not necessarily choose a neutral pH as the target when seeking to achieve a stable pharmaceutical formulation of ertapenem. The '820 patent simply does not teach a target pH range of 6.0 to 9.0. Defendant's attempt to fill in that missing limitation with the knowledge of a person of ordinary skill is insufficient. The

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[8] While all beta-lactams are hydrolytically unstable (Tr. 773:11-14), Dr. Stella opined that carbapenems were "more unstable than both the pencillins and cephalosporins, which were two types of precursor beta-lactams, more popular at the time." (Tr. 765:4-9).

[9] The parties agree that meropenem is, at least in some respects, structurally analogous to ertapenem. (Tr. 90:24-91:14, 909:16-23).

[10] Specifically, in the presence of nucleophilic buffers, the pH of maximum stability was 5 to 5.5, while in the presence of non-nucleophilic buffers, the pH of maximum stability was around 6. (Tr. 786:11-787:10).

evidence shows that a person of ordinary skill in the art would not necessarily target the pH range required to form the adduct.

To illustrate this point, Dr. Stella provided three scenarios where formulating the acidic forms of ertapenem, according to the teachings of the '820 patent, would not form the adduct. In Scenario 1, Dr. Stella describes blending the "EH3 plus" form of ertapenem with sodium bicarbonate in a one to one mole ratio. (Tr. 820:1-11). The resulting solution would have a pH about 4, which is within the range of maximum stability for hydrolytically unstable drugs like ertapenem. (Tr. 820:17-20). Because the pH in such a scenario would be below 6, the adduct would not form. (Tr. 820:12-16). In Scenario 2, Dr. Stella describes blending the zwitterion form of ertapenem with sodium bicarbonate in a one to one mole ratio. (Tr. 822:2-12). The resulting formulation would have a pH of about 5 to 5.5. (Tr. 822:4-12). As in Scenario 1, this is within the pH range of maximum stability for most hydrolytically unstable drugs. (Tr. 822:23-823:1). Since the pH is below 6, the adduct would not form. (Tr. 822:13-17). In Scenario 3, Dr. Stella describes blending the monoanion form of ertapenem with 10 mg or 15 mg of sodium bicarbonate per gram of ertapenem. (Tr. 824:6-18, 825:24-826:11). Once reconstituted in solution, the resulting formulation would have a pH of about 5.7. (Tr. 824:19-825:1). Since the pH would again be too low—and not enough ertapenem would exist in the dianion form—the adduct would not form in any detectable amount. (Tr. 824:22-825:8, 825:16-23).

Dr. Stella opined that all three scenarios were consistent with the '820 patent. (Tr. 820:4-16, 822:7-12, 825:24-826:11). Additionally, the formulations described in the scenarios would be suitable for administration to a patient. (Tr. 661:1-11, 821:17-21, 823:12-15, 827:5-11).

Defendant insists that these are extreme, "cherry-picked" scenarios, which are inconsistent with the teachings of the '820 patent. (D.I. 211 at pp. 7-8). Beyond the conclusory

testimony of Dr. Timko, Defendants have not provided any evidentiary basis upon which to conclude that these scenarios are inconsistent with the teachings of the '820 patent. In fact, Dr. Timko admitted that, while these are not the only possible scenarios, a skilled formulator could "possibly select th[e]se scenarios." (Tr. 668:4-670:7). "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *MEHL/Biophile*, 192 F.3d at 1365 (emphasis in original) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). "The disclosure [must be] sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function." *Id.* (quoting *In re Oelrich*, 666 F.2d at 581). Since the teachings of the '820 patent may or may not result in the formation of the adduct, there can be no inherent anticipation.

I conclude that Defendant has failed to show by clear and convincing evidence that the claimed invention is anticipated by the '820 patent.

B. Obviousness

i. Legal Standard

A patent claim is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406-07 (2007). The determination of obviousness is a question of law with underlying factual findings. *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012). "The underlying factual inquiries include (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any relevant secondary considerations . . . ." *Western Union Co. v. MoneyGram*

Payment Sys., Inc., 626 F.3d 1361, 1370 (Fed. Cir. 2010) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long-felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham*, 383 U.S. at 17-18; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662-63 (Fed. Cir. 2000); *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

A party asserting that a patent is invalid as obvious must "show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). That "expectation of success need only be reasonable, not absolute." *Id.* at 1364. "Whether an ordinarily skilled artisan would have reasonably expected success . . . . is measured as of the date of the invention[] . . . ." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

ii. Findings of Fact

1. The level of ordinary skill in the art is a scientist responsible for drug formulation, such as a pharmaceutical chemist, physical chemist, medicinal chemist, or organic chemist, involved in the research and development of pharmaceutical compounds. The person of ordinary skill would have either: (1) a Ph.D., in a field related to pharmaceutical formulation and

processing (such as pharmaceutical science, pharmacy, physical chemistry, organic chemistry, or pharmaceutics) and at least three years of experience in pharmaceutical compound development; or (2) a similar master's degree and at least five years experience in pharmaceutical compound development. Such an individual would also be familiar with or have access to the pertinent scientific literature.

2. The '820 patent, Smith I, the label for Primaxin, Takeuchi III, and Remington's are prior art.

3. No prior art reference recites the formation of a carbamate adduct causing stabilization of a drug product.

4. The claimed invention was commercially successful.

5. Defendant copied the asserted claims of the '323 patent.

6. No others tried and failed to create a stable formulation of ertapenem.

7. The results described in the '323 patent were unexpected.

8. There was not a long-felt need for a stable formulation of ertapenem.

9. A person of ordinary skill would not have had a reasonable expectation of success in stabilizing ertapenem.

10. The asserted claims of the '323 patent would not have been obvious to one of ordinary skill in the art.

iii. Conclusions of Law

a. Scope and Content of Prior Art

To show that the '323 patent would have been obvious to one of ordinary skill in the art, Defendant relies on five prior art references: the '820 patent, the Smith I paper, the label for

Primaxin,[11] the Takeuchi III paper, and the Remington's textbook. Smith I, Primaxin, and Takeuchi III all relate to other carbapenems, specifically meropenem and imipenem. The '820 patent, as discussed above, relates to ertapenem.

Smith I, a paper published in August 1980, discusses the stability of imipenem. (DTX 304; Tr. 910:8-11). Smith I teaches that the carboxylic acid groups in imipenem contribute to its degradation. (Tr. 858:5-18, 861:1-17). Smith also teaches that, at 20° C, imipenem is most stable between a pH of 6 and 7. (Tr. 910:12-14).

The label for Primaxin shows that imipenem was buffered with sodium bicarbonate "to provide solutions in the pH range of 6.5 to 8.5." (DTX 309 at p. 0007).[12] Further, the label states that "[t]here is no significant change in pH when solutions are prepared and used as directed." (*Id.*).

Takeuchi III, a paper published in April 1995, describes the stability and degradation of meropenem in aqueous solution. (DTX 303). Meropenem, like ertapenem, forms dimers at its pyrollidine nitrogen. (Tr. 900:19-901:14, 902:6-16). Such dimerization contributes to meropenem's degradation. (*Id.*). Takeuchi III also taught that meropenem was most stable in solution at a pH between 5 and 6. (Tr. 786:11-787:10, 788:17-22; DTX 303).

Remington's, a textbook published in 1985, teaches that adjusting pH may help optimize stability. (PTX 425 at p. 257). Remington's also acknowledges that "ideal conditions for maximum stability may be unacceptable from the viewpoint of pharmaceutically acceptable

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[11] Primaxin is Merck's brand name for its imipenem/cilastatin product.

[12] Plaintiff argues that this reference should not be considered, because it was published after the '323 patent's May 1996 priority date. (Tr. 684:17-685:4, 700:13-702:3). The label contains many dates, and I am not certain which information may have been reflected in the label which predates the '323 patent. Since I conclude that the label, in conjunction with Defendant's other references, does not render the claimed invention obvious, I will assume it is valid prior art for the obviousness analysis.

formulation or therapeutic efficacy, and it may be necessary to prepare a formulation with conditions less than optimum for stability of the drug." (*Id.*).

Plaintiff relies on Pratt, Archer, Yamana, Kovach, and the Takeuchi papers (I, II, and III) to show that the prior art taught away from the claimed invention. In Pratt, a beta-lactam molecule "reacts with . . . carbon dioxide to form a carbamate, but then the carbamate causes a rearrangement of the molecule." (Tr. 834:15-19; PTX 414). Thus, Pratt teaches the formation of the carbamate fundamentally changes the molecule. (Tr. 834:19-22). Similarly, Archer describes how the formation of a carbamate causes a rearrangement of a beta-lactam molecule, and thus "actually [leads] to degradation rather than stabilization." (Tr. 835:12-15, 836:8-11; PTX 413). Kovach, a paper published in 1975, also describes the formation of a carbamate. (Tr. Tr. 837:2-8; PTX 482). Kovach teaches that acetaminophen reacts with carbonate buffers to form a carbamate, which causes degradation. (Tr. 836-19:837:19).

Yamana, a paper published in 1977, states that a carbonate buffer, which reacted with the beta-lactam ring of a drug, was "the second most catalytic" of the buffers investigated. (Tr. 794:13-795:7; PTX 449). In other words, Yamana shows that carbonate, as a catalytic buffer, may cause degradation. (Tr. 828:2-14).

Takeuchi I and II teach that a dry blend of meropenem and sodium carbonate is stable. (Tr. 784:10-785:18; PTX 411; PTX 410). Those papers also teach, however, that when that dry blend is dissolved and then freeze-dried, the resulting product is extremely unstable. (Tr. 784:18-785:1, 786:3-7).

b. Comparison of the Prior Art and the Claimed Subject Matter

Defendant contends that the '323 patent is invalid as obvious over the '820 patent in light of the prior art references related to meropenem and imipenem. Defendant argues that these

prior art references "pointed like a beacon toward formulating ertapenem at neutral pH," and that under such conditions, the adduct would necessarily form. (D.I. 211 at p. 8). While none of these references expressly disclose the adduct, Defendant argues that "inherency . . . suppl[ies] [the] missing claim limitation in [the] obviousness analysis." *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194-95 (Fed. Cir. 2014). In other words, Defendant argues that the adduct is an "an inherent property" of an obvious formulation. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012); *see also In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011).

Plaintiff's cited prior art references do not teach that ertapenem should be formulated at neutral pH—i.e., under the conditions necessary for the adduct to form. A person of ordinary skill in the art would not have "a reasonable expectation of success in doing so." *Pfizer*, 480 F.3d at 1361. Instead, a person of ordinary skill in the art, at the time of invention, would have been faced, at best, with an array of inconclusive and sometimes contradictory teachings.

Defendant contends that "Takeuchi [III] taught that meropenem was more stable under neutral conditions." (D.I. 211 at p. 10 (citing DTX 303 at p. 0002)). To the contrary, Takeuchi III taught away from the patented invention, teaching that meropenem was most stable at a pH of 5 or 6. (Tr. 787:3-10, 788:17-22).[13] Takeuchi III also teaches that meropenem undergoes dimerization at around physiological pH.[14] (Tr. 798:2-9). Thus, to the extent one of skill in the art looked to the meropenem prior art for guidance, that person would expect that ertapenem would probably undergo that same reaction at around physiological pH. (*Id.*).

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[13] Defendant relies on the statement in Takeuchi III that meropenem "is relatively more unstable under acidic and alkaline conditions than under neutral condition[s], which is consistent with other β-lactam compounds." (DTX 303 at p. 0002). The data underlying this conclusion, as illustrated in Table 1, indicates that while this is generally true as a trend, the actual levels of maximum stability for meropenem are between 5 and 6. (*Id.*; *see also* Tr. 787:3-10, 788:17-22). This range is below the pH levels the '323 patent discloses as necessary for adduct formation.

[14] Physiological pH is about 7.4, though the parties use the term broadly to refer to pH values around 7. (Tr. 767:12-14, 775:9-15, 876:9-18).

Defendant argues that the prior art related to imipenem teaches formulating ertapenem at neutral pH. Defendant relies on Smith I, which generally teaches that imipenem is most stable between a pH of 6 and 7. (DTX 304 at pp. 0001-0002; Tr. 910:12-17). Defendant argues that Smith I also teaches that imipenem is unstable at low pH, and therefore, that a skilled artisan would expect ertapenem to be unstable at low pH. (D.I. 211 at pp. 9-10 (citing Tr. 861:1-17)). In support, Defendant cites to the testimony of Plaintiff's expert, Dr. Stella, arguing that he conceded this point. While Dr. Stella testified that Smith I and the '820 patent teach a skilled artisan that the carboxylic acid groups in ertapenem may contribute to instability, he did not testify that this had anything to do with low pH. (Tr. 861:1-17). Defendant also cites to the label for Primaxin as confirming to one of skill in the art that imipenem is most stable at a pH range of 6.5 to 8.5. (DTX 309 at p. 0007). Additionally, Defendant notes that the label discloses that the pH does not change during intravenous administration. (*Id.*). According to Defendant, this corroborates Remington's, which teaches that, "to be most suitable for injection, [a] solution should be about physiological[] pH." (D.I. 211 at p. 10). Altogether, according to Defendant, these references teach that, to achieve a stable drug product, imipenem should be formulated at a pH around neutral.

While the teachings related to imipenem may be instructive to one of ordinary skill in the art, there are important structural differences between imipenem and ertapenem, of which a person of ordinary skill would be aware. For instance, while imipenem may be isolated in crystalline form, the polyionizable character of ertapenem created difficulties in isolating a stable solid form. (Tr. 781:9-24). This led to the requirement that ertapenem be kept at -20° C in a freezer. (Tr. 781:17-782:2). Additionally, while imipenem is most stable at a pH between 6 and 7, that stability is not attributable to the formation of an adduct. (Tr. 779:6-15). In fact,

imipenem cannot form an adduct at all, since it has no pyrollidine nitrogen. (Tr. 779:6-781:5). Because of these differences, a skilled artisan would not reasonably expect that what had worked with imipenem would also work with ertapenem.

As discussed in the analysis of anticipation, the '820 patent does not mention any pH levels. As Dr. Stella's hypothetical scenarios demonstrate, the '820 patent does not guide a person of ordinary skill in the art toward formulating ertapenem at neutral pH.

Plaintiff argues that several prior art references taught away from the claimed invention. As illustrated in Pratt, Archer, and Kovach, the prior art taught that carbamate formation generally resulted in degradation. (Tr. 831:15-22). No prior art reference disclosed a carbamate adduct stabilizing a drug by preventing polymerization. (Tr. 829:22-830:8). Thus, a person of ordinary skill in the art would not have a reasonable expectation that the formation of a carbamate adduct would succeed in stabilizing ertapenem.

Therefore, the prior art does not teach an ordinary-skilled artisan to combine ertapenem with the requisite amount of bicarbonate/carbonate at a neutral pH, such that the adduct will form.

c. Secondary Considerations

"[S]econdary considerations, when present, must be considered in determining obviousness." *Ruiz*, 234 F.3d 654, 667; *see also Cyclobenzaprine*, 676 F.3d at 1076 ("[E]vidence on these secondary considerations is to be taken into account *always*, not just when the decisionmaker remains in doubt after reviewing the art." (internal quotation marks omitted) (quoting *Cable Elec. Prods. v. Genmark, Inc.*, 770 F.2d 1015, 1026 (Fed. Cir. 1985))). Here, Plaintiff has presented evidence of commercial success, copying, failure of others, unexpected results, and long-felt need.

1. Commercial Success

Both parties introduced expert testimony on commercial success. Defendant concedes that Plaintiff's Invanz product embodies the '323 patent. (D.I. 203 ¶ 3). Invanz generated $3.25 billion of sales worldwide and $1.8 billion of sales in the United States from 2002 to 2014. (Tr. 1012:20-1013:10; PTX 25; PTX 26). Invanz's sales and market share continually increased over that time period. (Tr. 1014:14-1015:11, 1016:12-1017:18, 1018:3-1019:8; PTX 25; PTX 27; PTX 28). Plaintiff's expert, Dr. Vellturo, opined that this growth was notable, given that several major antibiotics became available as generics during that period. (Tr. 1015:12-1016:11). In considering this evidence, Dr. Vellturo opined that Invanz has been a commercial success. (Tr. 1019:9-14).

Defendant's expert, Dr. Addanki, did not dispute that Invanz has been a commercial success, and instead focused his opinion on the nexus between Invanz's success and the '323 patent. (Tr. 710:12-24). "Evidence of commercial success . . . is only significant if there is a nexus between the claimed invention and the commercial success." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011) (omission in original) (quoting *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311-12 (Fed. Cir. 2006)). To show a nexus, a patentee must establish "that the sales were a direct result of the unique characteristics of the claimed invention." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996); *see also J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) (commercial success "must be due to the merits of the claimed invention beyond what was readily available in the prior art"). Dr. Addanki stated that Plaintiff's marketing materials focused on Invanz's clinical profile and once-daily dosing. (Tr. 713:20-715:1). Plaintiff's marketing materials did not mention the adduct, the manufacturing process, or the stabilized form. (*Id.*). This, according to Dr. Addanki, suggests

that the commercial success of Invanz is attributable to ertapenem itself, part of the prior art, rather than the stabilized form claimed in the '323 patent.

In response, Dr. Vellturo opined that, absent the '323 patent's stable formulation, and the '150 patent's manufacturing process, there would have been no product to market. (Tr 1021:2-1022:11). Defendant argues that this ignores several possible alternative methods for formulating a stable ertapenem product. For instance, Dr. Timko opined that ertapenem could have been developed as a "refrigerated product." (Tr. 644:18-645:21). Dr. Timko also referenced U.S. Patent No. 8,183,233 ("the '233 patent"), which discloses a method of stabilizing carbapenems by combining the carbapenem with water and a cyclodextrin, freezing that product, and later reconstituting it. (DTX 378; Tr. 645:22-647:7). The '233 patent explicitly mentions ertapenem as a "suitable pharmaceutical agent[] useful in embodiments of the present disclosure." (DTX 378 at 3:55-63). While this patent was issued in 2012, Dr. Timko opined that the technology described in the '233 patent would have been available in 1996. (Tr. 646:16-19).

I conclude that the commercial success of Invanz is sufficiently tied to the stable formulation described in the '323 patent. A company called Zeneca discovered the ertapenem compound. (Tr. 54:5-7).[15] In 1993, Zeneca granted Plaintiff an exclusive license to ertapenem. (Tr. 91:20-93:15, 718:23-719:8, 1036:1-16). According to Dr. Williams,[16] "Zeneca recognized that the development of a commercial process and a commercial formulation would be very difficult, and Merck had expertise in the development of carbapenems." (Tr. 54:8-55:13). Prior

[15] On October 4, 1993, Zeneca filed a U.S. patent application on ertapenem, and on December 26, 1995, the '820 patent issued. (DTX 19).

[16] Dr. Williams, a Merck employee, is a named inventor on the '323 patent. In December 1993, he, along with other Merck employees, met with the Zeneca employees who were responsible for the discovery of ertapenem. (Tr. 54:8-22).

to licensing ertapenem to Plaintiff, Zeneca determined that ertapenem was an unstable compound that required storage at -20° C. (Tr. 55:20-56:8). In particular, ertapenem was extremely unstable in solution,[17] such that "it under[went] decomposition . . . far too rapidly for administration in a hospital setting." (Tr. 59:13-60:10; *see also* Tr. 55:22-56:1). At the time Zeneca licensed ertapenem to Plaintiff, "a commercially viable formulation was not in place." (Tr. 56:9-58:12). The '323 patent solved this problem, and enabled Plaintiff to market a stable product. Therefore, the commercial success of Invanz was a result of the claimed invention.

The weight of the commercial success evidence is, however, discounted by the blocking effect of the '820 patent. Since ertapenem was claimed by the '820 patent, no entity aside from Zeneca, the original patentee, or Plaintiff, the exclusive licensee, had any incentive to develop a formulation for ertapenenem. (Tr. 718:23-719:8).[18] *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) ("Because market entry by others was precluded [due to patent protection and statutory exclusivity], the inference of non-obviousness . . . from evidence of commercial success . . . is weak."). Since the '820 patent blocked anyone other than Zeneca and Plaintiff from commercially exploiting ertapenem, no other industry players and the many persons of skill in the art employed by them had any incentive to develop alternative formulations for ertapenem. (Tr. 719:9-23). Therefore, while the stable formulation claimed by the '323 patent was commercially successful, the inference of non-obviousness from that fact is weak.

[17] Ertapenem must be in solution in order to be administered intravenously. (Tr. 59:24-60:10).
[18] Zeneca granted Plaintiff an exclusive license to the '820 patent, which covers the ertapenem compound. (Tr. 91:20-93:15).

2. Copying

"[C]opying by a competitor may be a relevant consideration in the secondary factor analysis." *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004). "[C]opying requires the replication of a specific product," which may be shown "through internal documents, direct evidence . . . or access to, and substantial similarity to, the patented product . . ." *Id.* (citations omitted). In the course of developing its generic product, Defendant considered "[u]sing different stabilizers other than carbon dioxide source (preferably Sodium chloride and/or Phosphate buffer)." (PTX 62 at p. 12). During development, Defendant tried at least five formulations that, according to Plaintiff, "would have avoided both the '323 and '150 patents because they used stabilizers that were not carbon dioxide sources." (D.I. 216 at p. 18). Instead, Defendant ultimately followed its "Primary Strategy," which was to use "[l]yophilization to obtain a stable product (reversible carbon dioxide adduct) using the process as per U.S. Patent 6486150B2," *i.e.*, the '150 patent. (PTX 62 at p. 12). This is evidence of copying. Defendant argues that copying is "not compelling evidence of nonobviousness" in a Hatch-Waxman case, since a generic drug manufacturer is required to copy the approved drug. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 676 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014). Defendant is correct that 21 U.S.C. § 355(j)(2)(A) requires a generic to copy the active pharmaceutical ingredient of the reference drug, and to establish bioequivalency. The generic is not, however, required to copy inactive ingredients or the methods used in a manufacturing process. *Dey, L.P. v. Teva Parenteral Meds., Inc.*, 6 F. Supp. 3d 651, 681 (N.D.W. Va. 2014). Defendant's decision to copy Plaintiff's formulation and process "is an indicium of nonobviousness." *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 679 (Fed. Cir. 1988).

3. Failure of Others

Plaintiff argues that because Zeneca licensed ertapenem to Plaintiff, it must have failed to make its own stable formulation, thereby showing the failure of others. (D.I. 216 at pp. 18-19). Specifically, Dr. Williams and Dr. Vellturo infer that, because Zeneca licensed ertapenem to Plaintiff, it could not find a way to create a stable formulation of ertapenem. (Tr. 58:6-12, 105:208, 1023:15-16). This is far too speculative. There are many reasons why a company might not choose to undertake the process of taking an active pharmaceutical ingredient and developing a final formulated product. (Tr. 721:2-722:12). Plaintiff has not advanced evidence suggesting that anyone tried, and failed, to formulate stable ertapenem.

4. Unexpected Results

Plaintiff maintains that the formation of the adduct, with its associated stabilizing effect, constitutes an unexpected result. Dr. Williams, one of the inventors, testified that the stabilizing effect of adding bicarbonate was "a very surprising result," as he and the other inventors "had no reason to expect that bicarbonate would suppress the [formation] of dimers in solutions of ertapenem." (Tr. 66:8-21). Dr. Kaufman, another inventor, stated that he and the other inventors believed that sodium bicarbonate would function as an inert buffer. (Tr. 302:4-23). Defendant argues that the prior art reveals that carbamate adduct formation in solutions containing amines and carbon dioxide was well known. (D.I. 211 at p. 14 (citing Tr. 102:23-103:13)). Dr. Williams acknowledged this fact. (Tr. 102:23-103:13). Defendant also notes that carbamate adducts were known to form with other pharmaceutical compounds, such as penicillin. (Tr. 103:18-104:7, 650:11-652:12). Even assuming that the formation of the adduct was expected, the stabilizing effect of the adduct was unexpected. As explained earlier, adduct formation was known to cause degradation in prior art products, rather than an increase in stability. (*See, e.g.*,

Tr. 792:10-793:12). Thus, "[t]he unexpected properties of the claimed formulation, even if inherent in that formulation, differ in kind from the prior art, thereby supporting a conclusion of nonobviousness." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015); *see also In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."). In other words, "the previously unknown and unexpected properties of a new and nonobvious formulation constitute additional, objective evidence of nonobviousness." *Allergan*, 796 F.3d at 1307 (emphasis omitted).

5. Long-Felt Need

Plaintiff argues that Invanz satisfied a long-felt need. Plaintiff's expert, Dr. Solomkin, testified that, although existing carbapenems fulfilled certain needs, they required frequent infusions and had "too broad a spectrum." (Tr. 995:23-996:11). Dr. Stella testified that it would take "a high degree of creativity" to come up with an alternative formulation for ertapenem, but acknowledged that it was possible. (Tr. 850:7-18). Defendant contends that meropenem is very similar to ertapenem and satisfied whatever needs ertapenem fulfilled. (D.I. 211 at p. 14). Dr. Solomkin agreed that other carbapenems had similar antibiotic efficacy. (Tr. 992:18-22). Plaintiff argues that since ertapenem is not active against Pseudomonas bacteria, while meropenem is (Tr. 992:18-994:5), there is a long-felt need for ertapenem. I do not follow that argument. Perhaps there is some advantage to having one carbapenem for Pseudomonas and another for community-acquired infections, but that does not strike me as constituting a long-felt need. Additionally, ertapenem requires only one intravenous infusion per day, while meropenem requires three. (Tr. 989:3-8). This reduces the complexity of care, by requiring less nursing and pharmacy time, and increases efficacy, by maximizing the amount of time that the

concentration of the antibiotic within the blood is above the minimum effective concentration level. (Tr. 989:11-990:4). There is also a small safety benefit because of the risk of "potentially contaminated infusions." (Tr. 989:17-21). On balance, I am not convinced that there was a long-felt need for ertapenem.

There is also the issue of nexus. The satisfaction of any long-felt need described by Plaintiff is attributable to ertapenem, not to the stable formulation described in the '323 patent. Therefore, there is no "nexus between the evidence and the merits of the claimed invention." *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995). Plaintiff again argues that ertapenem would not be commercially available but for the '323 patent, but has failed to advance sufficient evidence to support that conclusion. I think there is a difference between "commercial success" and "commercial availability." The stable formulation may be necessary for commercial success. I do not see it as necessary for commercial availability. A "refrigerated product" would not have been a commercial success, but there is no reason why, if there was a long-felt need, it could not have been made commercially available.

d. Conclusion

This case does not present a scenario "where a skilled artisan merely pursues 'known options' from a 'finite number of identified, predictable solutions.'" *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *KSR*, 550 U.S. at 421). Rather, this is a situation "where a defendant [has] merely throw[n] metaphorical darts at a board filled with combinatorial prior art possibilities." *Id.* Where, as here, a researcher is confronted with numerous variables and possibilities, and lacks adequate guidance from the prior art, it cannot be said that a particular combination was accompanied by "a reasonable expectation of success." *Pfizer*, 480 F.3d at 1361. Defendant argues that the prior art taught a person of ordinary skill to formulate

ertapenem at neutral pH, and, in doing so, a person of ordinary skill would have had a reasonable expectation of stabilizing ertapenem. I cannot agree.

If, at the moment before invention, a voice whispered to the inventors, "Do you think it'll work?" the answer would most likely have been, "I don't know." This is, at least in part, because neither the inventors, nor anyone else, had any understanding of the adduct's ability to stabilize ertapenem. Relatedly, and more importantly, the prior art did not lead a person of ordinary skill in the art to the conditions described in the '323 patent as a solution. In other words, the prior art did not teach a skilled artisan to combine ertapenem with bicarbonate/carbonate at a neutral pH. Thus, this is not a case where the prior art's "express teachings render the claimed . . . formulation obvious, and the claimed [adduct] adds nothing of patentable consequence." *Kao*, 639 F.3d at 1070; *see also Kubin*, 561 F.3d at 1357. The adduct is not merely an inherent property of an obvious formulation. Accordingly, Defendant has failed to show that the adduct is "the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharm.*, 773 F.3d at 1196.

Having considered the framework for obviousness laid out in *Graham* and *KSR*, I conclude that Defendant has failed to show by clear and convincing evidence that the claimed invention would have been obvious to one of ordinary skill in the art.

C. Written Description

i. Legal Standard

Section 112 ¶ 1 "contains a written description requirement separate from enablement." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "[T]he description must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Id.* (alteration in original) (quoting *Vas-Cath Inc. v. Mahurkar*, 935

F.2d 1555, 1563 (Fed. Cir. 1991)). "[T]he test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* "[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* "Whether the description requirement is met is a question of fact . . . ." *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985).

ii. Findings of Fact

The level of ordinary skill in the art is a scientist responsible for drug formulation, such as a pharmaceutical chemist, physical chemist, medicinal chemist, or organic chemist, involved in the research and development of pharmaceutical compounds. The person of ordinary skill would have either: (1) a Ph.D., in a field related to pharmaceutical formulation and processing (such as pharmaceutical science, pharmacy, physical chemistry, organic chemistry, or pharmaceutics) and at least three years of experience in pharmaceutical compound development; or (2) a similar master's degree and at least five years experience in pharmaceutical compound development. Such an individual would also be familiar with or have access to the pertinent scientific literature.

iii. Conclusions of Law

The '323 patent teaches that the carbamate adduct cannot form outside the pH range of 6.0 to 9.0. Defendant contends that because method claims 4 through 6 lack any limitation pertaining to pH, the claims are not commensurate in scope with the disclosures in the specification. Put another way, Defendant argues that the claims, which contain no pH

limitation, are broader than what is described in the specification, and are therefore invalid for lack of written description.

Defendant specifically relies on *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473 (Fed. Cir. 1998). There, the applicant attempted to amend claims to capture subject matter not described in the specification. Specifically, the applicant "identifie[d] the console as the only possible location for the controls" on a reclining sectional sofa. *Id.* at 1479. The disclosure thus "limited [the claims] to sofas in which the recliner control [was] located on the console." *Id.* The applicant was therefore not entitled to claims where the recliner controls were not located on the console. *Id.* at 1479-80. In short, the Federal Circuit concluded that "claims may be no broader than the supporting disclosure, and therefore that a narrow disclosure will limit claim breadth." *Id.* at 1480; *see also Cooper Cameron Corp. v. Kvaerner Oilfield Prods.*, 291 F.3d 1317, 1323 (Fed. Cir. 2002) (stating that *Gentry Gallery* "applied and merely expounded upon the unremarkable proposition that a broad claim is invalid when the entirety of the specification clearly indicates that the invention is of a much narrower scope").

Defendant's reliance on *Gentry Gallery* is misplaced. The patentee was not required to include a pH limitation in the claims of the '323 patent. There is no "'essential element' test mandating an inquiry into what an inventor considers to be essential to his invention and requiring that the claims incorporate those elements." *Cooper Cameron*, 291 F.3d at 1323. The key question is instead whether the claims "overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Ariad*, 598 F.3d at 1353-54; *see also Cooper Cameron*, 291 F.3d at 1323. Here, since the adduct does not form outside the pH range of 6.0 to 9.0, the omission of pH from the claims has no effect on the scope of the claims. (Tr. 851:14-852:8; *see also* PTX 1 at 2:14-20; Tr. 53:6-22, 652:20-653:4). Therefore, claims 4

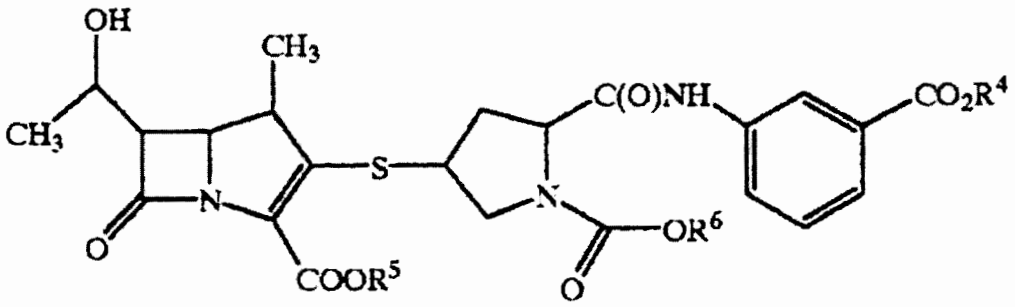
through 6 do not broaden the scope of the claims beyond the '323 patent's description. The '323 patent's disclosure therefore "reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter." *Ariad*, 598 F.3d at 1351.

II. '150 PATENT

Independent claim 21 of the '150 patent reads:

A process for preparing a final formulation product of a compound of formula Ia,

Ia



or its pharmaceutically acceptable salt, or hydrates wherein, R^4, R^5, and R^6 are independently:

(a) hydrogen

(b) (C_1–C_6)-alkyl, or

(c) alkali-metal or alkali earth-metal wherein the alkali-metal or alkali earth-metal is sodium, potassium, lithium, cesium, rubidium, barium, calcium or magnesium;

comprising the steps of:

(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;

(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about -3° C to about 15° C.;

(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content.

(PTX 2 at 18:11-43). Dependent claims 22 through 34 contain numerous narrowing limitations, the substance of which is discussed in the validity analysis of those claims.

A. Claim Construction

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (internal quotation marks omitted). "'[T]here is no magic formula or catechism for conducting claim construction.' Instead, the court is free to attach the appropriate weight to appropriate sources 'in light of the statutes and policies that inform patent law.'" *SoftView LLC v. Apple Inc.*, 2013 WL 4758195, at *1 (D. Del. Sept. 4, 2013) (quoting *Phillips*, 415 F.3d at 1324). When construing patent claims, a court considers the literal language of the claim, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977-80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Of these sources, "the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (internal quotation marks and citations omitted).

"[T]he words of a claim are generally given their ordinary and customary meaning. . . . [Which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312-13 (internal quotation marks and citations omitted). "[T]he ordinary meaning of a claim term is its meaning to [an] ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted). "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314 (internal citations omitted).

When a court relies solely upon the intrinsic evidence—the patent claims, the specification, and the prosecution history—the court's construction is a matter of law. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 841 (2015). The court may also make factual findings based upon consideration of extrinsic evidence, which "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317-19 (internal quotation marks and citations omitted). Extrinsic evidence may assist the court in understanding the underlying technology, the meaning of terms to one skilled in the art, and how the invention works. *Id.* Extrinsic evidence, however, is less reliable and less useful in claim construction than the patent and its prosecution history. *Id.*

"A claim construction is persuasive, not because it follows a certain rule, but because it defines terms in the context of the whole patent." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It follows that "a claim interpretation that would exclude the inventor's device is rarely the correct interpretation." *Osram GmbH v. Int'l Trade Comm'n*, 505 F.3d 1351, 1358 (Fed. Cir. 2007) (internal quotation marks and citation omitted).

The Court held a Markman hearing on July 30, 2015. (D.I. 137). At that time, the Court offered a preliminary construction of the term "the final formulation product of a compound of formula Ia." (*Id.* at 95-96). The Court determined that the term required that the process "achieve the stabilized form of carbon dioxide [or, carbamate] adduct in the final composition" by "'a high rate conversion' . . . from the carbapenem salt to the carbon dioxide adduct." (*Id.*). The parties now dispute what is meant by "a high rate conversion," as it relates to the final formulation product. Plaintiff contends a "'high rate conversion' is a rate that results in a mixture of ertapenem and the carbon dioxide adduct with the latter present in an amount

sufficient to stabilize the formulation and provide for a low level of degradants." (D.I. 210 at pp. 4-5). Put another way, "high rate conversion" is defined functionally as a conversion which provides "low by-product formation." Defendant, framing its argument in a slightly different way, argues that "the final formulation product of a compound of formula Ia" should be construed as "a lyophilized product resulting from about 80% conversion to the carbamate." (D.I. 217 at p. 6). In other words, Defendant argues that "a high rate conversion" is a conversion where 80% of the carbapenem salt is converted to the adduct.

The '150 patent does not explain what percentage of adduct, converted from the carbapenem salt, would constitute a "high rate conversion." (Tr. 187:24-188:4). To divine the meaning of the term, the parties focus on one passage from the specification, where the '150 patent explains that "[t]he present process provide[s] a high rate conversion from the alkali metal salt, such as monosodium salt of carbapenem[,] to the carbon dioxide adduct and the low by-product formation, such as dimers and open ring compounds." (PTX 2 at 9:13-17). Plaintiff argues that this means the "high rate conversion" describes the way in which the patent achieves its "low by-product formation" result. Defendant argues that the use of the word "and" in the "and the low by-product formation" phrase indicates that "[l]ow by-product formation is a feature that is separate from, and in addition to, high rate conversion to the adduct." (D.I. 217 at p. 7). In other words, Defendant argues that the '150 patent's specification describes two goals: (1) a high rate conversion, and (2) a process of minimizing degradation. (*Id.*; Tr. 416:5-417:15).

Read as a whole, the '150 patent's specification suggests that the proper construction is that the "high rate conversion" is the means of achieving low by-product formation. The specification includes four examples of the claimed invention. In each of these examples, the specification includes information about the total amounts of degradants, dimers, and open ring

compounds. (PTX 2 at 12:20-15:63 tbls. 2, 4, & 7; *see also* Tr. 188:15-24). The specification does not explain what percentage of carbapenem is converted into the adduct. Nor does the '150 patent mention any level of adduct which is required to achieve these low levels of degradants. (Tr. 187:15-23). Rather, a high rate conversion is simply a conversion wherein enough of the adduct was formed so that the resulting final formulation products were stable, with low levels of degradants. (Tr. 221:16-20). The focus of the invention is on minimizing degradants through a conversion, rather than maximizing the amount of salt which is converted. This reading finds further support elsewhere in the specification. In the Background of the Invention, the '150 patent notes that the prior art "fail[ed] to teach how to achieve the conversion of salt-containing carbapenem compound to a formulation exhibiting acceptable levels of degradates required for solid state and reconstitution stability for dosing to patients." (PTX 2 at 2:30-38). This confirms that the goal of the invention, and of the high rate conversion, was to minimize degradants.

In support of its construction, Defendant relies solely on the testimony of its expert, Dr. Murgatroyd. Without citing to any documents, Dr. Murgatroyd opines that a high rate conversion means an 80 percent yield. (Tr. 405:23-406:17, 440:22-441:1, 509:1-9). This figure finds little support in the patent's specification, the prosecution history, or the claims. (*See* Tr. 508:10-19, 510:9-16). Dependent claim 24, which depends from independent claim 21, claims a "mole ratio of carbon dioxide source to the active ingredient [of] about 0.5 to about 1.5." (PTX 2 at 18:52-56). As conceded by Dr. Muragtroyd, a 0.5 ratio of carbon dioxide source to active ingredient could not produce a yield higher than 50%. (Tr. 497:16-498:4). Thus, Defendant proposes a construction which excludes a dependent claim from the scope of the independent claim from which it depends. To put it another way, Defendant argues that the "final formulation product" claimed in claim 21 means at least an 80 percent yield. (Tr. 405:23-

406:13). Since dependent claim 24 contemplates a yield as low as 50%, Defendant's construction would exclude that dependent claim from the scope of the claim from which it depends. This construction should be avoided. *See, e.g.*, *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("It is axiomatic that a dependent claim cannot be broader than the claim from which it depends"); *Intamin Ltd. v. Magnetar Techs., Corp.*, 483 F.3d 1328, 1335 (Fed. Cir. 2007) ("An independent claim impliedly embraces more subject matter than its narrower dependent claim.").

I therefore adopt Plaintiff's construction. A "high rate conversion" is construed as "a rate that results in a mixture of ertapenem and the carbamate adduct with the latter present in an amount sufficient to stabilize the formulation and provide for a low level of degradants."

B. Infringement

i. Legal Standard

"Under [35 U.S.C.] § 271(e)(2)(A), a court must determine whether, 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). The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001). Literal infringement is present only when each and every element set forth in the patent claims is found in the accused product.[19] *See Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575-76 (Fed. Cir. 1995). The patent owner has 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). Infringement can be shown by "any method of analysis that is probative of the fact of

[19] There are no assertions of infringement by the doctrine of equivalents.

infringement," and, in some cases, "circumstantial evidence may be sufficient." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009).

ii. Findings of Fact

Defendant's ANDA product contains amounts of the carbamate adduct sufficient to stabilize the formulation and provide for a low level of degradants.

iii. Conclusions of Law

Defendant agrees that every limitation of claims 21-34 is satisfied, other than the "final formulation product" limitation. (D.I. 203 ¶ 1). Thus, the only question is whether the adduct is "present in an amount sufficient to stabilize the formulation and provide for a low level of degradants." Defendant concedes that its product contains the adduct. (*Id.* ¶ 14). Both Plaintiff and Defendant "have used . . . processes . . . which resulted in cakes that had low enough levels of . . . degradants that they met specifications." (Tr. at 218:12-220:9, 512:16-514:13; *see also* PTX 479; PTX 550).

The amount of adduct in Defendant's product is sufficient to reduce dimer formation and provide a stable product.[20] Therefore, Defendant's product satisfies the "final formulation product" limitation. Defendant's ANDA product will thus be made by a process which literally infringes the asserted claims of the '150 patent.[21]

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[20] To detect the amount of adduct in Defendant's lyophilized product, both parties rely on nitrogen-15 solid state nuclear magnetic resonance testing. The parties dispute which data, and which analysis, accurately reflects the level of adduct in Defendant's product. Properly construed, the "final formulation product" limitation does not require any quantification. Therefore, I need not and do not resolve these disputes.

[21] "To be sure, if at the end of the day, an act that would have been an infringement . . . pertains to a patent that is shown to be invalid, there is no patent to be infringed." *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1929 (2015). Since I ultimately conclude that the '150 patent is invalid as obvious, there is ultimately no infringement.

C. Obviousness

i. Findings of Fact

1. The level of ordinary skill in the art is either (1) a person with a Ph.D. in organic chemistry, medicinal chemistry, chemical engineering, or a related discipline, and two to five years of experience; or (2) a person with a lesser degree with additional work experience. Additionally, a person of ordinary skill in the art would understand the relevant chemical literature.

2. The '323 patent and Almarsson are prior art.

3. The '323 patent and Almarsson both teach that the formation of the adduct is dependent on pH, and that formation of the adduct requires a pH range of about 6.0 to about 9.0.

4. The '323 patent and Almarsson both teach that sodium hydroxide could be used to adjust pH.

5. The '323 patent and Almarsson both teach that the carbamate adduct could be produced using lyophilization.

6. A person of ordinary skill in the art would have known that temperature was a result-effective variable.

7. The optimization of the temperature range for the reaction would have been routine to one of ordinary skill in the art.

8. Plaintiff's product, which utilizes the claimed process, is a commercial success.

9. Defendant copied the manufacturing process recited in the asserted claims of the '150 patent.

10. There was not a long-felt need for the manufacturing process described in the asserted claims of the '150 patent.

11. The asserted claims of the '150 patent would have been obvious to a person having ordinary skill in the art.

ii. Conclusions of Law

Defendant contends that the '150 patent is invalid as obvious under two separate bases: (1) it is obvious over the '323 patent in light of the knowledge of a skilled artisan, and (2) it is obvious over the Almarsson patent application in light of the knowledge of a skilled artisan.

The parties have presented similar definitions for a person of ordinary skill in the art. For Defendant, Dr. Murgatroyd testified that a person of ordinary skill would have "a Ph.D. in a field related to pharmaceutical formulation and processing, and probably about three years experience in the field of the pharmaceutical industry, and with a Master's, probably five years experience." (Tr. 393:10-15). For Plaintiff, Dr. Stahly opined that a person of ordinary skill "would be someone with a Ph.D. degree in organic chemistry, maybe medicinal chemistry, chemical engineering, or related discipline, and in addition would need probably two to five years of experience." (Tr. 180:4-12). Dr. Stahly also stated that it was "possible someone could be skilled in the art without the Ph.D., but they would have needed additional work experience." (Tr. 180:13-18). In either case, Dr. Stahly testified that a person of ordinary skill "would [also] have to know how to utilize and understand the chemical literature." (Tr. 180:16-18). Dr. Murgatroyd stated that, even if the Court adopted Dr. Stahly's definition, his opinion would not change. (Tr. 393:24-394:5). I do not think the difference in definitions is material to the outcome. I adopt Dr. Stahly's definition.

a. Claim 21

As indicated above, claim 21 of the '150 patent discloses a manufacturing process for "preparing a final formulation product." The steps are:

(1) charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel;
(2) adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about -3° C. to about 15° C.;
(3) lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content.

(PTX 2 at 18:32-43).

1. '323 Patent

Defendant contends that claim 21 is obvious over the '323 patent in light of the knowledge of a skilled artisan. A skilled artisan, armed with the "recipe" taught by the '323 patent, Defendant argues, would have found claim 21 of the '150 patent obvious.

The '323 patent taught that ertapenem was unstable, and that stability was related to pH. (Tr. 395:12-396:1, 397:7-399:16). Specifically, the '323 patent taught that "stabilization occurred in the pH range from about 6 to 9." (Tr. 816:22-817:1, 431:24-432:11; PTX 1 at 2:14-20). This was a "sweet spot" because the solution would not suffer from destabilizing hydrolysis, and the formation of the carbamate would prevent the polymerization reaction. (Tr. 817:7-19).

The '323 patent also explained that "[o]ther compounds c[ould] be included to adjust the pH of the composition upon dilution or reconstitution." (PTX 1 at 3:15-18). The '323 patent provided several examples, including sodium hydroxide. (*Id.* at 3:17-18).

The '323 patent discloses that the carbamate adduct may be produced using "standard lyophilization techniques." (Tr. 957:12-20; PTX 1 at 3:38-40).

The steps recited in claim 21 are an obvious implementation of the '323 patent into a manufacturing process. Step (1) recites "charging a solution of carbon dioxide source having a pH range of about 6.0 to about 12.0 into a reaction vessel." (PTX 2 at 18:33-35). A skilled

artisan, seeking to follow the teachings of the '323 patent, would begin a manufacturing process by creating a solution of carbon dioxide source at a pH of 6 to 9. (Tr. 422:5-423:10). As explained by Dr. Murgatroyd, by first adjusting the pH of the carbon dioxide source, ertapenem—which is sensitive to pH—may be added directly to a solution that is at the preferred pH. (Tr. 424:13-425:11). This minimizes the amount of time that ertapenem spends in solution at unstable pH levels. (*Id.*).

Step (2) recites "adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of carbon dioxide source to maintain pH at about 6.0 to about 9.0 and a temperature range of about -3° C. to about 15° C." (PTX 2 at 18:36-40). After creating a solution of a carbon dioxide source and water at stable pH, a skilled artisan would add the active ingredient. (Tr. 437:10-15). In doing so, a skilled artisan would seek to maintain the pH of ertapenem in solution at a pH between about 6 to about 9, since that is precisely what was taught by the '323 patent. (Tr. 431:24-432:11; PTX 1 at 2:14-20). The '323 patent explicitly notes that a base, such as sodium hydroxide, can be be used to adjust the pH of the composition. (PTX 1 at 3:15-18; Tr. 438:9-23). The '323 patent does not disclose the simultaneous addition of sodium hydroxide and ertapenem. A skilled artisan, however, would know that the monosodium salt of ertapenem sodium has a pH of about 5.5. (Tr. 425:18-24, 870:7-10, 886:20-23). Thus, to counteract the acidifying effect of the ertapenem salt—and thus keep the solution pH in the target range—a skilled artisan would simultaneously add a base, such as sodium hydroxide. (Tr. 423:11-22, 928:9-16).

Lower temperatures tend to slow most degradation reactions, while higher temperatures tend to accelerate degradation reactions. (Tr. 423:23-424:12). This is widely known to those of skill in the art. (Tr. 89:20-90:12, 423:23-424:12, 924:22-925:8). Since a person of ordinary skill

would know of ertapenem's tendency to degrade, that person would seek to chill the solution of ertapenem to a low temperature. (Tr. 438-24-439:11). Specifically, a person of ordinary skill in the art would attempt to cool the solution to reach the lowest possible temperature without freezing.[22] (*Id.*, Tr. 467:4-16; *see also* Tr. 439:5-11). Dr. Murgatroyd therefore opined that a person of ordinary skill in the art would have arrived at the claimed temperature range. (Tr. 467:2-21). "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (alteration in original) (quoting *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955));[23] *see also KSR*, 550 U.S. at 421 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.").

Step (3) requires "lyophilizing the solution of Step (2) to yield the final formulation product of a compound of formula Ia with less than about 10% of moisture content." (PTX 2 at 18:41-43). The lyophilization process is important, as it removes the water from the composition, thereby stabilizing the remaining solid material. (Tr. 929:15-20; *see also* Tr. 426:5-20). Claim 21 does not specify any particular lyophilization conditions. (PTX 2 at 18:41-43; Tr. 977:6-11). Dr. Murgatroyd opined that a moisture content of 0.5 percent to 3.0 percent was common at the time of invention. (Tr. 427:16-430:5; *see* also DTX 359 at pp. 34-35).

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[22] Since ertapenem causes a depression in the freezing point of water, an ertapenem solution maintained at a temperature slightly below 0° C would not freeze. (Tr. 467:11-16).

[23] "This rule is limited to cases in which the optimized variable is a 'result-effective variable.'" *Id.* (quoting *In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977)). In this case, there is little doubt that the results of temperature manipulation were recognized by those of skill in the art, as acknowledged by Drs. Williams, Murgatroyd, and Stahly. (Tr. 89:20-90:12, 423:23-424:12, 924:22-925:8).

Further, Dr. Muragtroyd testified that a skilled artisan would be able to achieve a moisture content below 10% with routine optimization. (Tr. 427:16-430:5).[24]

Properly construed, the "final formulation product" limitation requires adduct formation sufficient to stabilize the final formulation product. By Plaintiff's own admission, the '323 patent teaches compositions with adduct formation sufficient to stabilize the product, such that it is suitable for administration to patients by injection. (Tr. 878:10-879:6).

Plaintiff's expert, Dr. Stahly, opined that "the steps, the order of the steps, the details of how each step is carried out are not presented in [the '323] patent." (Tr. 942:7-18). I conclude that the order of the steps would have been obvious to a person of skill in the art. Dr. Stahly concedes that adding the active ingredient without the base present "would drive the pH down, and it would lead to protonation of pyrollidine amine, so that the adduct would not form, and it would also be in a region where hydrolysis would be faster." (Tr. 928:9-16). If, in order to adjust the pH of the solution, the base was added before the active ingredient, "that would drive the pH higher, and then when the active ingredient went in, . . . hydrolysis would be faster than desired." (Tr. 928:17-24). If all three ingredients were placed in solution at the same time, the resulting "uncontrolled situation" with "many competing reactions" would be expected to create "high levels of degradants." (Tr. 929:1-9). The '323 patent may not explicitly lay out the steps claimed in the '150 patent, but that is not what an obviousness inquiry requires. "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR*, 550 U.S. at 421. Indeed, "[i]n *KSR*, the Supreme Court criticized a rigid approach to determining obviousness based on the disclosures of individual prior-art references, with little recourse to the knowledge, creativity, and common sense that an ordinarily skilled artisan would have brought to bear when

[24] While lyophilization parameters are product-specific (Tr. 930:18-24), claim 21 does not specify any particular lyophilization conditions.

considering combinations or modifications." *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013); *see also KSR*, 550 U.S. at 418 ("The analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.").

Claim 21 is a general recitation of routine manufacturing steps which would have been obvious to one of ordinary skill in the art. A person of ordinary skill, seeking a manufacturing process for the compound disclosed in the '323 patent, would predictably arrive at the solution described in the '150 patent, and would reasonably expect that it would succeed. In other words, "the differences between [claim 21] and [the '323 patent] are such that claim 21 as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103. I conclude that Defendant has made a *prima facie* showing that claim 21 is obvious over the '323 patent.

2. Almarsson

Defendant contends that claim 21 is obvious over Almarsson in light of the knowledge of a skilled artisan. Almarsson is an international patent application filed by Plaintiff's employee Örn Almarsson. (DTX 294). Since Almarsson's disclosures are very similar to those of the '323 patent, Defendant's theory of obviousness is similar.

Like the '323 patent, Almarsson discloses the parameters required for the formation of the adduct: (1) a pH range of "about 6.0 to about 9.0," or preferably, "about 6.2 to about 8.5;" (2) using sodium carbonate or bicarbonate in the same ratios with the active ingredient; (3) adjusting the pH with a base, such as sodium hydroxide; and (4) lyophilizing "using standard lyophilization techniques." (DTX 294 at pp. 14-15, 22-23; *see also* PTX 1 at 2:14-20, 3:8-40).

Just as these disclosures rendered claim 21 obvious when taught by the '323 patent, they render claim 21 obvious here.

In addition to these disclosures, Almarsson includes data about the stability of ertapenem in solution. (DTX 294 at p. 31). Dr. Murgatroyd explained that the graph from Example 3 shows that ertapenem in solution at pH 7.5 and a temperature of 5° C, in the absence of carbonate, undergoes dimerization at a constant rate. (*Id.*; Tr. 448:16-449:21). The graph also shows that, under the same conditions, the presence of carbonate, a carbon dioxide source which results in the formation of the adduct, causes dimer formation to stop after an initial period. (DTX 294 at p. 31; Tr. 448:16-449:21). The "carbonate-buffered" formulation, under solid state conditions at 25° C, remained stable for "twelve or more weeks." (DTX 294 at p. 31). According to Dr. Murgatroyd, this additional data about temperature provides "a good indication . . . to keep the temperature low . . . [to] slow down degradant reactions." (Tr. 449:16-21). Further, the data on dimer formation shows that the bicarbonate, by forming the adduct, "protect[s] against dimer formation." (Tr. 449:10:15).

I therefore conclude that Defendant has made a *prima facie* showing that claim 21 is obvious over Almarsson.

b. Claims 22-34

Defendant argues that dependent claims 22 through 34 are obvious over both the '323 patent and Almarsson. "[E]ach claim must be considered as defining a separate invention." *Jones v. Hardy*, 727 F.2d 1524, 1528 (Fed. Cir. 1984). "Each claim . . . shall be presumed valid independently of the validity of the other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim." 35 U.S.C. § 282. This "independent evaluation is necessary because dependent claims necessarily add limitations to the

claims from which they depend . . . ." *Dana Corp. v. Am. Axle & Mfg., Inc.*, 279 F.3d 1372, 1376 (Fed. Cir. 2002).

The dependent claims add several narrowing limitations to steps (1) and (2). Claim 22 requires that the carbon dioxide source be selected from a particular list. (PTX 2 at 18:44-49). Claim 23 recites that the carbon dioxide source is sodium bicarbonate. (*Id.* at 18:50-51). Claims 24 and 25 recite specific mole ratios of the carbon dioxide source to an active ingredient: about 0.5 to about 1.5, and about 0.8 to about 1.2, respectively. (*Id.* at 18:52-61). Claim 26 and 27 narrow the pH range and temperature range recited in step (1) to a pH range of about 7.0 to about 9.0, and a temperature range of about -3° C to about 15° C. (*Id.* at 62-65). Claim 28 defines the active ingredient as ertapenem. (*Id.* at 18:66-19:11; Tr. 199:12-18, 460:2-7)). Claim 29 requires that the base be selected from a particular list. (PTX 2 at 19:12-20). Claim 30 narrows the base of step (2) to about 1N to about 3N of sodium hydroxide. (*Id.* at 19:21-22). Claims 31 and 32 recite specific mole ratios of the base to an active ingredient: about 0.7 to about 1.0, and about 0.8 to about 0.9, respectively. (*Id.* at 19:23-28). Claims 33 and 34 narrow the pH range and temperature range recited in step (2) to a pH range of about 7.0 to about 8.0, and a temperature range of about -1° C to about 5° C. (*Id.* at 19:19-20:2).

Dr. Murgatroyd opined that each of these claims would have been obvious in view of both the '323 patent and Almarsson. As to claims 22, 23, 24, and 25, the '323 patent and Almarsson disclose sodium bicarbonate as a carbon dioxide source in a one-to-one molar ratio with ertapenem. (Tr. 456:13-458:5). Claims 26 and 27 would have been obvious to one of ordinary skill for the same reasons the claimed pH and temperature ranges in step (2) of claim 21 were obvious. (Tr. 458:9-459:6). Since the '323 patent and Almarsson teach ertapenem as an active ingredient, claim 28 also would have been obvious. (Tr. 460:5-13). Dr. Murgatroyd

opined that claims 29 and 30 would have been obvious to one of skill in the art, as the '323 patent and Almarsson disclosed using sodium hydroxide to adjust pH. (Tr. 460:18-461:14). While Dr. Murgatroyd noted that claim 30's specific concentrations were not disclosed in either the '323 patent or Almarsson, he opined that the recited concentrations—a range of one to three normal—were commonly used by persons of ordinary skill, in order to minimize pockets of extreme pH. (Tr. 461:11-463:11). Dr. Murgatroyd opined that claims 31 and 32 would have been obvious, as an artisan of ordinary skill would, in practicing the '323 patent or Almarsson, "automatically" arive at the claimed mole ratios. (Tr. 463:10-465:7).[25] According to Dr. Murgatroyd, claim 33 would have been obvious, as the '323 patent and Almarsson teach a pH range of about 6 to about 9, and arriving at a narrower range would have been routine optimization to one of skill in the art. (Tr. 465:16-466:13). Similarly, the narrower temperature range claimed in claim 34 would have been obvious, through routine optimization, to an ordinary-skilled artisan seeking to minimize degradation. (Tr. 466:22-467:21).

While the validity of each claim rises or falls independently, Plaintiff did not provide any evidence in support of each dependent's claim validity. Rather, Plaintiff focused entirely on the validity of claim 21. Thus, Dr. Murgatroyd's invalidity testimony on the dependent claims' additional limitations was not disputed.

I conclude that Defendant has made a *prima facie* showing that claims 22-34 of the '150 patent are invalid as obvious.

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[25] Dr. Murgatroyd explains that, as ertapenem is added to a solution with a pH of about between 6 and 9, the solution will become more acidic. (Tr. 464:1-8). Thus, to raise the pH, thereby cancelling out the effect of the ertapenem, one would add the appropriate amount of base. (Tr. 464:8-465:1). The "end result" of this "would be the correct mole ratio," as specified in claims 31 and 32. (Tr. 465:2-7).

c. Secondary Considerations

Plaintiff argues that all of the evidence of commercial success, copying, and long-felt need discussed in connection with the '323 patent also applies with respect to the '150 patent.

The discussion of commercial success, copying, and long-felt need, with respect to the formulation described in the '323 patent, applies with equal force to the manufacturing process claimed in the '150 patent. In summary, Plaintiff has not shown evidence of long-felt need, but has shown evidence of copying and commercial success.[26] While the copying and commercial success evidence supports the argument for non-obviousness, "secondary considerations of nonobviousness . . . simply cannot overcome a strong prima facie case of obviousness." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010).

Having considered the framework for obviousness laid out in *Graham* and *KSR*, I conclude that claims 21-34 of the '150 patent would have been obvious to one of ordinary skill in the art.

D. Anticipation

i. Findings of Fact

1. The level of ordinary skill in the art is either (1) a person with a Ph.D. in organic chemistry, medicinal chemistry, chemical engineering, or a related discipline, and two to five years of experience; or (2) a person with a lesser degree with additional work experience. Additionally, a person of ordinary skill in the art would understand the relevant chemical literature.

2. The Tsinontides manuscript is prior art.

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[26] I previously concluded that the '820 patent's effect as a blocking patent weakened the evidence of commercial success with respect to the stable formulation claimed in the '323 patent. I conclude the same with respect to the manufacturing process recited in the '150 patent.

3. The Tsinontides manuscript does not disclose charging a solution of carbon dioxide source, having a pH range of about 6.0 to about 12.0, into a reaction vessel.

4. The Tsinontides manuscript does not disclose adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of a carbon dioxide source.

5. The Tsinontides manuscript does not anticipate the '150 patent.

ii. Conclusions of Law

Defendant argues that slide presentation authored by inventor Stelios Tsinontides ("the Tsinontides manuscript"), and presented at a conference in 1999, anticipates claims 21 through 29. The parties first dispute whether the Tsinontides manuscript qualifies as prior art. Since I conclude that the Tsinontides manuscript does not anticipate claims 21 through 29 of the '150 patent, I need not address the question of whether the manuscript qualifies as prior art. I will accept, for purposes of the anticipation analysis, that the Tsinontides manuscript is 35 U.S.C. § 102(b) prior art.

Defendant argues that, although the exact words of claim 21 do not appear in the manuscript, it discloses the substance of the claimed invention. (Tr. 477:3-24; D.I. 211 at p. 30). I disagree. The slides only generally describe the problems that the '150 patent sought to solve. For instance, slide 16 refers to the "[b]alancing [a]ct" of controlling dimerization and ring-opening hydrolysis. (PTX 269 at p. 16). In that slide, Dr. Tsinontides explains that "[m]anufactring [l]osses" may be "[m]inimize[d]" by forming the adduct with carbon dioxide from carbonate, adjusting pH with sodium hydroxide, and using a "[r]apid [c]ompounding [p]rocess at 5° C." (*Id.*). The slide also refers to three different lyophilized formulations: .84, 1.0, and 1.25 mole-equivalents of carbonate. (*Id.*). On slide 17, Dr. Tsinontides indicates that he

had achieved moisture contents of about 2%. (*Id.* at p. 17). Slide 22 refers to the same formulations described in slide 16. (*Id.* at p. 22). The chart on slide 22 shows experimental results which reflect the level of carbonate at the three different stages of initial charging, pre-lyophilization, and the final product. (*Id.*).

The slides do not describe the process recited in claims 21 through 29. While a "reference need not satisfy an *ipsissimis verbis* test," the reference "must disclose each and every element of the claimed invention," with those elements "'arranged or combined in the same way as in the claim.'" *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009) (quoting *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008)). The Tsinontides manuscript does not describe any steps, the details of those steps, or the order of those steps. There is no mention of any process involving "[c]harging a solution of carbon dioxide source, having a pH range of about 6.0 to about 12.0 into a reaction vessel." (PTX 2 at 18:33-35). The presentation similarly fails to disclose "adding an effective amount of a mole ratio of a base and an active ingredient into the reaction vessel containing the solution of a carbon dioxide source." (*Id.* at 18:36-38). The manuscript sheds some light on the process ultimately claimed in the '150 patent, but it does not disclose the elements of claim 21. (Tr. 938:19-941:6).

Since the Tsinontides manuscript does not anticipate claim 21, it cannot anticipate claims 22 through 29, which depend from claim 21. *See Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("[A] dependent claim narrows the claim from which it depends [and] must 'incorporate . . . all the limitations of the claim to which it refers.'" (omission in original) (quoting 35 U.S.C. 112 ¶ 4)).

Therefore, Defendant has failed to show, by clear and convincing evidence, that the Tsinontides manuscript anticipates claims 21 through 29 of the '150 patent.

III. CONCLUSION

Defendant failed to prove by clear and convincing evidence that any of the asserted claims of the '323 patent are invalid. Defendant proved by clear and convincing evidence that asserted claims 21 through 34 of the '150 patent are invalid as obvious.

Plaintiff should submit an agreed upon form of final judgment within two weeks.