NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

VALEANT PHARMACEUTICALS INTERNATIONAL, INC. et al.,	
Plaintiffs,	Civil Action No. 15-8180 (SRC)
v.	**OPINION & ORDER**
MYLAN PHARMACEUTICALS, INC. et al.,	
Defendants.	

CHESLER, U.S.D.J.

This matter comes before the Court on the motion for partial summary judgment, pursuant to Federal Rule of Civil Procedure 56, by Plaintiffs Progenics Pharmaceuticals, Inc., Salix Pharmaceuticals, Inc., Valeant Pharmaceuticals International, Inc., and Wyeth LLC (collectively, "Plaintiffs.") For the reasons stated below, the motion will be granted.

This is a Hatch-Waxman case involving a patent dispute regarding pharmaceuticals: the complaints in these consolidated cases allege that Defendants Mylan Inc., Mylan Laboratories Ltd., Mylan Pharmaceuticals, Inc., and Actavis LLC (collectively, "Defendants") seek to make and sell a generic version of Plaintiff's Relistor® (methylnaltrexone bromide) pharmaceutical product prior to the expiration of the relevant patents. Plaintiffs' motion concerns claim 8 of United States Patent No. 8,552,025 (the "'025 patent"). '

Plaintiffs move for partial summary judgment on Defendants' affirmative defense to infringement of invalidity due to obviousness. Plaintiffs contend that, as to claim 8, Defendants cannot prove invalidity due to obviousness. Claim 8 depends on claim 1:

1. A stable pharmaceutical preparation comprising a solution of methylnaltrexone or a salt thereof, wherein the preparation comprises a pH between about 3.0 and about 4.0.

8. The pharmaceutical preparation of claim 1, wherein the preparation is stable to storage for 24 months at about room temperature.

Defendants contend that claim 8 is invalid due to obviousness. Defendants cite these prior art references:

1. "Foss 2001" (Deni Dec. Ex. 2). This journal article reports on clinical studies of methylnaltrexone, including intravenous administration. It is undisputed that Foss 2001 "does not explicitly mention storage stability or degradation issues for methylnaltrexone." (Defs.' 56.1 Stmt. at SOF #60.)

2. "Yuan 2000" (Deni Dec. Ex. 28.) This journal article reports on a clinical study of methylnaltrexone, including intravenous administration. It is undisputed that "Yuan 2000 does not explicitly mention storage stability or degradation issues for methylnaltrexone." (Defs.' 56.1 Stmt. at SOF #65.)

3. "Foss '954" (Deni Dec. Ex. 3.) U.S. Patent No. 5,972,954 covers methods of use of methylnaltrexone for medical treatment. It is undisputed that "Foss '954 does not explicitly mention storage stability or degradation issues for methylnaltrexone." (Defs.' 56.1 Stmt. at SOF #70.)

4. "Gibson" and "Remington" are general pharmaceutical formulation references. There is no dispute about Dr. Khan's statement that Gibson and Remington "provide a number of ways to stabilize a parenteral preparation, such as optimizing the pH, adding antioxidants, chelating agents, and a variety of stabilizers." (Khan Opening Report at ¶ 113; Defs.' 56.1 Stmt. at SOF #75, #80.)

5. "Bahal '154" (Deni Dec. Ex. 6.) U.S. Patent No. 5,866,154 discloses stable preparations of naloxone hydrochloride. The patent abstract states:

> Physically and chemically stable pharmaceutical compositions useful for administering naloxone by injection are described. These compositions are essentially aqueous solutions having a pH between 3.0-3.5, and containing naloxone, an acidic or buffer component, a tonicity adjusting agent, and a stabilizing agent, said composition being optionally sterilized by autoclaving.

Defendants state: "The prior art Bahal '154 reference disclosed a stable solution of naloxone that had a pH of 3.2 and contained a chelating agent (EDTA) as a

stabilizer." (Defs.' Opp. Br. 24.) "Bahal '154 also teaches stabilizing the composition by using stabilizing agents such as sodium edetate, citrate, EDTA, and inert gas (e.g., nitrogen)." (Khan Opening Rpt. ¶ 148.) This reference was before the examiner during prosecution of the '025 patent. (Defs.' 56.1 Stmt. at SOF # 83.)

6. "Oshlack '111" (Deni Dec. Ex. 7.) The abstract of U.S. Patent Publication No. 2003/0229111 states: "The present invention relates to compositions and methods of stabilizing naltrexone hydrochloride." It discloses oral dosage forms, not injectables. (Defs.' 56.1 Stmt. at SOF # 95.) This reference was before the examiner during prosecution of the '025 patent. (Defs.' 56.1 Stmt. at SOF # 93.)

7. "Fawcett 1997" (Abe Dec. Ex. 3.) This journal article reports on a clinical study of naltrexone which found, *inter alia*, that oral solutions have a shelf life of 60 days or less, under various conditions.

In moving for summary judgment, Plaintiffs make three arguments: 1) Defendants have failed to identify any motivation to modify the prior art methylnaltrexone products; 2) Defendants cannot establish that the "stable to storage for 24 months" element was known in the prior art; and 3) Defendants cannot prove their "obvious to try" theory.

As to the first argument, Plaintiffs contend that saline solutions of methylnaltrexone were known in the prior art, but that there is no evidence that the prior art recognized any stability problems with them. Plaintiffs assert that Defendants have defined the problem by its solution, revealing the operation of impermissible hindsight. In opposition, Defendants contend that the prior art had not attempted commercial development of methylnaltrexone saline solutions, and that it was the commercial development process that produced both recognition of the stability problem, and its solution in the '025 patent. In reply, Plaintiffs contend that Defendants "have identified no credible motivation to modify the prior art." (Pls.' Reply Br. 1.) Plaintiffs' point is unpersuasive. In fact, Defendants have pointed to the motive of commercial pharmaceutical development of a product known in the prior art to have utility as a pharmaceutical. It is

completely apparent – and Plaintiffs do not dispute this – that, in the prior art, skilled artisans were already actively engaged in a process of pharmaceutical development. Although this Court ultimately agrees with Plaintiffs that Defendants cannot prove invalidity due to obviousness, Plaintiffs' first argument does not address Defendants' point of failure. It is not as if pharmaceutical uses of methylnaltrexone saline solutions were unknown in the prior art: the title of the prior art Foss patent is "Use of methylnaltrexone and related compounds to treat chronic opioid use side affects [*sic*]." U.S. Patent No. 6,559,158. Plaintiffs do not contend that the '025 patent covers a new use for methylnaltrexone saline solutions. The motivation to engage in commercial pharmaceutical development of known pharmaceuticals is, for lack of a better word, obvious. "[M]otivation to combine may be found explicitly or implicitly in market forces." Plantronics, Inc. v. Aliph, Inc., 724 F.3d 1343, 1354 (Fed. Cir. 2013). People generally are motivated to make commercial use of inventions like the Foss patent. This is not the weak link in Defendants' obviousness case.

Plaintiffs next contend that Defendants have no evidence that establishes that the element of "stable to storage for 24 months at about room temperature" was disclosed in the prior art. Plaintiffs argue that this alone is fatal to Defendants' obviousness case "because to prove obviousness, the prior art references must set forth every element of the asserted claim." (Pls.' Br. 13.) This is an incorrect statement of the law of obviousness, which does not impose the "every element" requirement found in the law of anticipation. It may be correct that, as Plaintiffs contend, none of the prior art cited by Defendants discloses a pharmaceutical solution that is stable for 24 months at about room temperature. That is not, however, fatal to Defendants' obviousness case. No one contends that the inventors invented a 24-month shelf life, which was previously

unknown in the art.[1] As the Supreme Court explained in KSR:

> As our precedents make clear, however, 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. . . . The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418-19 (2007). Plaintiffs argue as if the law required Defendants to show precise teachings directed to every element of the challenged claim; it does not. KSR allows a court to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." Id. As Defendants' expert, Dr. Khan, stated:

> A POSA would have known that a drug dissolved in saline and administered to patients for the purpose of evaluating drug efficacy, unlike commercial products, are not necessarily intended for the longer storage time. Thus, a POSA would consider storage and shipment stability as part of routine drug product development after clinical studies have shown the drug to be safe and effective.

(Khan Reply Rpt. ¶ 26.) Defendants thus have evidence that supports the inference that the skilled artisan, engaged in routine commercial drug development, would employ the creative step of formulating the drug product for a longer storage time.

While the absence of a prior art reference disclosing this element of claim 8, "stable to storage for 24 months at about room temperature," is not fatal to Defendants' obviousness case, as Plaintiffs contend, it does point to a particular challenge for Defendants. Based on the record

[1] Defendants point to the 2003 version of the ICH guidelines, "Stability Testing of New Drug Substances and Products," which requires studies of long-term storage stability, with a minimum duration of twelve months, and contemplates a longer duration if needed to cover the proposed shelf life. (Abe Dec. Ex. 6 at § 2.2.7.) This is sufficient, at summary judgment, to support the inference that long-term stability testing of new pharmaceutical products was well-known in the prior art.

before this Court, the prior art did not teach how to formulate an injectable pharmaceutical solution that is stable for 24 months. Defendants have offered no evidence to the contrary. Thus, while the *idea* of an injectable pharmaceutical solution stable for 24 months seems unlikely to have been unknown, there is no evidence before this Court that the art taught how to make one. The evidence of record shows that the prior art taught a variety of techniques for improving the stability of such solutions, but there is no evidence that anyone had ever achieved an injectable pharmaceutical solution stable for 24 months. This frames the challenge for Defendants: to show the path that a skilled artisan, faced with the problem of formulating an injectable solution of methylnaltrexone with long-term stability, would take, in order to reach the invention of claim 8, in the absence of prior art that taught how to stabilize an injectable pharmaceutical solution for that length of time.

With that in mind, we turn to Plaintiff's third argument, which succeeds. Plaintiffs contend that Defendants rely on an "obvious to try" theory, but lack the evidence to support such a theory. Within this argument, Plaintiffs make two principal points: 1) Defendants have failed to prove a reasonable expectation of success; and 2) Defendants have failed to show a finite number of identified, predictable solutions.

Defendants, in opposition, agree that their defense of invalidity due to obviousness relies on an "obvious to try" theory. Defendants argue, however, that material disputes about underlying facts preclude a grant of summary judgment.

In KSR, the Supreme Court held that obviousness may be proven using an "obvious to try" theory when certain conditions are present:

> 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. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR, 550 U.S. at 421. The Federal Circuit has further explained:

> To be sure, to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1365 (Fed. Cir. 2007).

Defendants first argue that factual disputes exist regarding the obviousness of the claimed pH range of 3-4. Defendants cite In re Peterson, 315 F.3d 1325, 1329 (Fed. Cir. 2003), which held: "A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art." Defendants contend that the pH range of 3-4 overlaps the ranges disclosed in the prior art, pointing to Dr. Khan's opening expert report. In that report, Dr. Khan pointed to the pH ranges in three pieces of prior art: Bahal '154, Oshlack '111, and Fawcett 1997. (Khan Rpt. ¶¶ 98-102.) Dr. Khan states that Bahal '154 discloses a solution of naloxone for parenteral administration (¶ 99), Oshlack '111 discloses a solution of naltrexone for oral administration (¶ 102), and Fawcett 1997 discloses a solution of naltrexone for oral administration (Id.).

On this point, Defendants' opposition brief offers no discussion of the law, or the facts, or the application of the law to the facts; this Court is not persuaded. Not one of the three cited pieces of prior art teaches the use of methylnaltrexone in any form. The Court wonders: does *any* piece of prior art teaching *any* composition with a pH range of 3-4 raise a *prima facie* case of obviousness? The answer is no, because you do not have an overlapping range when the prior art

composition is not the same composition. In Haynes, the Federal Circuit clearly articulated the method for comparison: "when the difference between the claimed invention and the prior art is the range or value of a particular variable, then a prima facie rejection is properly established when the difference in range or value is minor." Haynes Int'l, Inc. v. Jessop Steel Co., 8 F.3d 1573, 1577 n.3 (Fed. Cir. 1993). Thus, for the principle of overlapping ranges to apply, the difference between the claimed invention and the prior art must be the range or value of a particular variable.[2] The differences between claim 8 and each of the prior art references (Bahal '154, Oshlack '111, and Fawcett 1997) is greater than the value of the pH variable. This Court is not persuaded, as a matter of law, that any of the cited prior art references which teach the use of naloxone and naltrexone presents an overlapping pH range sufficient to make out a *prima facie* case of obviousness.

Next, Defendants next make a series of points that can be addressed briefly because they are peripheral: 1) "a POSA would test for pH related stability and would be motivated to optimize the pH profile" (Defs.' Opp. Br. 9); 2) "a POSA would understand that saline solutions are not intended for long term storage" (Defs.' Opp. Br. 10); "pH is known to affect stability and other properties of solution;" (Def's Opp. Br. 12); and "[t]he structures of naloxone and naltrexone differ from methylnaltrexone only in the substituents attached to the tertiary amine."[3] (Defs.' Opp.

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[2] See also Iron Grip Barbell Co. v. USA Sports, Inc., 392 F.3d 1317, 1322 (Fed. Cir. 2004) ("where there is a range disclosed in the prior art, and the claimed invention falls within that range, there is a presumption of obviousness.") Defendants have here presented no evidence that the claimed invention – a methylnaltrexone solution – can be said to fall within the pH ranges for naloxone or naltrexone solutions in the prior art.

[3] It is undisputed that the chemical structure of methylnaltrexone differs from both that of naloxone and that of naltrexone. (Defs.' 56.1 Stmt. # 35, 37.) At the same time, it is also undisputed that, according to Defendant's chemistry expert, Dr. Hunter, other than enantiomers

Br. 16.) The Court need not closely examine these points because they are not essential to the "obvious to try" analysis – they form the foundation, not the main point. In any case, Defendants have certainly offered evidence in support of these points. For purposes of this motion, the Court infers all of these facts in favor of the non-movant, Defendants.

With this foundation, Defendants proceed to their main argument: a pH range of 3 to 4 would have been obvious to try. Defendants argue first that the possible approaches to solving the problem of long-term storage of methylnaltrexone solutions were known and finite.[4] Defendants argue: "A pH of 3 to 4 was just one of a finite number of options of pH ranges falling between 3 and 7." (Defs.' Opp. Br. 20.) This is simply false: given any two unequal numbers, the quantity of number ranges falling between the two is infinite, not finite. This is basic math.

Defendants assert: "the fact remains that adjusting pH would be the first variable most experienced formulators would consider." (Defs.' Opp. Br. 20 n.7.) Defendants then cite to a number of pieces of evidence, none of which supports the assertion. First, Defendants quote from the Gibson treatise: "[S]olution pH is one of the major determinants of the stability of the

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(which are not implicated in this case), active pharmaceutical ingredients with different chemical structures have different physical and chemical properties. (Defs.' 56.1 Stmt. # 40.)

[4] The Court recognizes that, in the decision that Defendants cite, the Federal Circuit stated: "The [Supreme] Court explained that when the problem is known, *the possible approaches to solving the problem are known and finite*, and the solution is predictable through use of a known option, then the pursuit of the known option may be obvious even absent a 'teaching, suggestion, or motivation' concerning that option." Abbott Labs. v. Sandoz, Inc., 544 F.3d 1341, 1351 (Fed. Cir. 2008) (italics added). This Court need not today deal with the matter of the difference in word choice (where KSR speaks of a finite number of "solutions," Abbott speaks of a finite number of "approaches.") In Abbot, the Federal Circuit stated clearly that "the *KSR* standard [is] whether the patents in suit represented an 'identified, predictable solution' and 'anticipated success.' Id. at 1352; see also Rolls-Royce, PLC v. United Techs. Corp., 603 F.3d 1325, 1339 (Fed. Cir. 2010) ("The important question is whether the invention is an 'identified, predictable solution' and an 'anticipated success.')

compound." (Deni Dec. Ex. 4 at 35.) This statement manifestly does not say anything about the formulation process. A few sentences later, Gibson states: "it is prudent to adjust the pH to the desired value to optimize stability." (Id.) This statement deals with the formulation process, but cannot reasonably be understood to assert that adjusting pH would be the *first* variable formulators would consider to improve stability; Gibson calls it "prudent," not "primary." Defendants next cite to a paragraph in Dr. Hunter's expert report which says only: "The pH of a pharmaceutical formulation can have an impact on the stability of the formulation."[5] (Abe Dec. Ex. 2 at ¶ 40.) Lastly, Defendants cite to a paragraph in the reply report of Dr. Khan, which states that development of a stable commercial product "would include optimizing the pH and using excipients." (Abe Dec. Ex. 9 at ¶ 27.) Defendants here have pointed to no evidence that "adjusting pH would be the first variable most experienced formulators would consider."

A related problem appears in Defendants' Rule 56.1 Statement. Defendants there contend that Dr. Khan expressed the opinion "that optimizing the pH would be one of the leading candidates to resolve stability issues." (Defs.' 56.1 Stmt # 46, citing Deni Dec. Ex. 25 at 157:4-10.) This is not false, but it is misleading. Here is the cited exchange:

> Q: It is your opinion that one of ordinary skill in the art would have expected pH to be one of the leading candidates for resolving stability issues along with excipients, such as stabilizers, antioxidants, and kelating agents, correct?
>
> A: Correct.

(Deni Dec. Ex. 25 at 157:4-10.) In the testimony Defendants rely on, Dr. Khan stated that pH, stabilizers, antioxidants, and chelating agents form the group of leading candidates for resolving

[5] Moreover, Dr. Hunter is a chemist, not a formulator.

stability issues. This is consistent with his statement in his opening report: "A POSA would know of several established means to keep the degradation amount below the claimed amount." (Deni Dec. Ex. 8 at ¶ 148.) The Khan Report then lists, as established means: using antioxidants or chelating agents, stabilizers, and optimizing the pH. (Id.) The point here is that, in the cited testimony, Dr. Khan did not identify adjusting pH as the primary approach to adjusting formulation stability. Instead, he placed it in a group of leading approaches with a number of other members.[6]

Defendants next argue: "Arriving at a pH of 3.0 to 4.0 (acidic) for the long-term stability of a methylnaltrexone solution was a predictable result." (Defs.' Opp. Br. 21.) This is a crucial underlying factual proposition for Defendants' obviousness case. In support, Defendants rely heavily on paragraph 76 in the Khan Reply Report:

> 76. Dr. Williams asserts that a POSA would not have had a reasonable expectation of success that the pH ranges for naloxone or naltrexone would stabilize methylnaltrexone. Williams Rebuttal Report at ¶¶ 105, 119. I disagree. As discussed above and in my opening report, a POSA would have found relevant the teachings of Bahal '154, Oshlack '111, and Fawcett 1997, because of 1) the structurally similarities of these compounds, 2) the common potential for hydrolytic degradation, 3) understanding that naloxone or naltrexone formulations were stable at acidic pH, and 4) quaternary ammonium compounds were also known to degrade in basic pH. Thus, a POSA would have expected that formulations of methylnaltrexone with an acidic pH would provide stable formulations. See supra

[6] The parties agree that adjusting pH was one of a number of options in the prior art for improving stability under these circumstances. The parties' L. Civ. R. 56.1 factual statements show that it is undisputed that a skilled artisan, faced with the problem of formulating a stable injectable methylnaltrexone solution, would have at least six options to consider: pH, stabilizers, antioxidants, chelating agents, container closure system, and preservatives. (Defs.' 56.1 Stmt # 46; Deni Dec. Ex. 25 at 157:4-158:11.) Defendants seem to suggest that adjusting pH was the leading option, but no evidence supports this. In the absence of evidence that optimizing pH was the leading option for improving stability, as Plaintiffs contend, Defendants have "retraced the path of the inventor with hindsight." Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008).

¶¶ 20-53; Khan Opening Report at ¶¶ 98-105, 120-26, 176-82.

The Court need not examine Dr. Khan's reasoning here in detail because Dr. Khan's conclusion falls way short of showing that the invention was a predictable result. Dr. Khan concludes here that "a POSA would have expected that formulations of methylnaltrexone with an acidic pH would provide stable formulations." This is insufficient in two ways. First, "formulations of methylnaltrexone with an acidic pH" does not equate to "a pH between about 3.0 and about 4.0," as stated in claim 1. Second, "stable formulations" does not equate to "stable to storage for 24 months at about room temperature," as stated in claim 8. Even if a finder of fact were to fully credit Dr. Khan's conclusion, as expressed in paragraph 76, this would not be sufficient evidence to support a finding that the invention of claim 8 was a predictable result. Dr. Khan's conclusion does not go farther than to say that the skilled artisan would have expected that formulations of methylnaltrexone with an acidic pH would have unspecified stability. There is a large gap between this expected result and claim 8, which is directed to a formulation of methylnaltrexone with a pH between about 3.0 and about 4.0 that is stable to storage for 24 months at about room temperature. Defendants also rely heavily on the deposition testimony of Dr. Williams. (Williams 1/16/18 Dep. Tr. at 70-77.) It is puzzling that Defendants offer this section of testimony, since Dr. Williams states that the skilled artisan would not have had any information on stability based on the two Foss prior art references. (Id. at 70:15-71:11.) Dr. Williams goes on to discuss what the skilled artisan would have understood from the teachings of Bahal '154, and he reads from the Bahal reference:

> Ready to use injectable solution formulations of naloxone with improved chemical and physical stability are preferably composed of an effective amount of naloxone hydrochloride, an acid or a buffer to yield a final solution pH of 3 to 3.5, in one or more tonicity adjusting agents, and a stabilizing agent . . .

(Id. at 76:11-17.) Defendants offer this as evidence in support of the inference that "a POSA would have used the pH range for naloxone and naltrexone with methylnaltrexone and expect a similar, satisfactory stability for that product." (Defs.' Opp. Br. 22.) The cited deposition testimony does not support that inference. In the cited testimony, Dr. Williams pointed only to the disclosure in Bahal that a naloxone solution with a final solution pH of 3 to 3.5 would have "improved" stability. Dr. Williams points to nothing that further characterizes whatever stability was observed, and there is no basis for an inference that Bahal disclosed naloxone solutions with "satisfactory" stability (under any definition), much less stability for a 24-month period.

Nor do the prior art references themselves support the inference that "a POSA would have used the pH range for naloxone and naltrexone with methylnaltrexone and expect a similar, satisfactory stability for that product." Three prior art references deal with naloxone or naltrexone: Bahal '154, Oshlack '111, and Fawcett 1997. Bahal '154 teaches this discovery: "It has now been found that addition of a chelating agent, such as sodium edetate, to the commercial formulation prevents naloxone degradation, even in the presence of oxygen and after autoclaving." (Bahal '154, col.1 ll.54-57.) The "summary of the invention" section states: "More particularly, the compositions contain an effective amount of naloxone, an acidic or buffer component to give a pH of the final composition of 3-3.5, a stabilizing agent, and a tonicity-adjusting agent, said composition being autoclaved." (Bahal '154, col.1 l.67-col.2 l.4.) Bahal '154 does not discuss at any point the role of pH in stability. Rather, Balah '154 discusses the effect of stabilizing agents, such as sodium edetate, on stability. Defendants have not pointed to any disclosure in Bahal '154 which indicates that a pH of 3-4 improves the stability of a naloxone solution.

As to Oshlack '111, it teaches the use of stabilizers and chelating agents to stabilize oral

dosage forms of naltrexone. Claims 34, 35, and 36 contain pH limitations. The only mention of pH in the specification appears in the "Detailed Description of the Invention." After a series of disclosures about the use of stabilizers to inhibit the degradation of naltrexone, the reference states:

> [0054] In certain embodiments, the stabilizer is dissolved or dispersed in a solution prior to mixing the stabilizer with the naltrexone hydrochloride. Thereafter, it may be necessary to adjust the pH of the solution or dispersion of the stabilizer to provide for a stabilized naltrexone hydrochloride composition. In certain preferred embodiments, the pH of the solution or dispersion of the stabilizer is adjusted to about 3 to about 5, preferably about 4.

(Oshlack '111 at ¶ [0054].) Oshlack '111 thus does not at any point disclose the use of pH alone to stabilize naltrexone solutions.

Fawcett 1997 describes a study which looked at the stability of a liquid for oral administration for a period of 90 days or less. The oral liquid was prepared from naltrexone tablets or powder, to which ascorbic acid, sodium benzoate, and glycerol were added. (Abe Dec. Ex. 3 at 1292.) The reference makes only one statement about pH: "In all cases the pH fell slightly from 3.5 to 3.2 over 90 days." (Id. at 1293.) Defendants have not identified what Fawcett 1997 teaches that would have predicted the success of claim 8 in the patent at issue.

Defendants have not persuaded this Court that any of the prior art references dealing with naloxone and naltrexone – that is, Bahal '154, Oshlack '111, and Fawcett 1997 – taught something that would have made claim 8 a predictable result.

The cited evidence from Dr. Khan and Dr. Williams does not support a finding that, as Defendants assert, for the skilled artisan, "[a]rriving at a pH of 3.0 to 4.0 (acidic) for the long-term stability of a methylnaltrexone solution was a predictable result." No reasonable trier of fact could

hear this evidence and arrive at that conclusion.[7] Nor do the contents of the cited pieces of prior art support that conclusion. This is a crucial underlying factual proposition for Defendants' obviousness case, and Defendants have failed to offer evidence from which a reasonable jury could find this to be true.

Third, Defendants contend that they have evidence that the skilled artisan had a reasonable expectation of success in formulating a methylnaltrexone solution that is stable to storage for 24 months at about room temperature. Defendants begin their discussion by claiming to have evidence which supports their assertion of a reasonable expectation of success, but the five pages of discussion that follow do not point it out. Defendants first criticize the absence of stability data in the '025 patent, which is irrelevant to their point.

Next, Defendants contend that Dr. Khan stated that, "based on the accelerated stability data in Bahal '154, a POSA would have reasonably expected that *such a formulation* would be able to achieve room temperature storage stability for a far longer period, including for at least 24 months." (Defs.' Opp. Br. 24; italics added) This sounds promising, but actually says far less than Defendants would like. It is fair to say that Dr. Khan opined that, based on the accelerated stability data in Bahal '154, a skilled artisan would have expected longer stability based on "such a formulation," *i.e.*, the formulations taught by Bahal '154. The problem is that Bahal '154 did not teach the use of pH 3-4 to stabilize naloxone solutions; rather, Bahal '154 taught the use of

[7] In this context, it bears repeating that, based on the evidence of record, the prior art did not teach injectable pharmaceutical solutions with 24-month stability. Thus, for the invention of claim 8 to have been contemplated as a predictable result, there must be evidence of a basis to predict that something that had never been accomplished before could be accomplished. In the absence of such evidence, calling claim 8 a predictable result shows the operation of hindsight.

stabilizers such as sodium edetate to stabilize naloxone solutions.[8] Defendants have not yet pointed to any statements from Dr. Khan which show how the skilled artisan, reading Bahal '154, would have reasonably expected success in achieving the formulation disclosed in claim 8.

Defendants next contend: "Dr. Khan explained that a POSA would have reasonably expected similar results from structurally similar compounds, such as methylnaltrexone." (Defs.' Opp. Br. 25.) Again, this statement says less than Defendants would like. Results similar to Bahal '154 would include stabilization of structurally similar compounds through the use of stabilizers such as sodium edetate. Defendants have not persuaded that, based on the Bahal reference, which teaches the use of sodium edetate to stabilize naloxone solutions, the skilled artisan would have expected a methylnaltrexone formulation lacking sodium edetate to be stable.

The bottom line is that this section of Defendants' brief points to no evidence supporting an inference that claim 8 was a predictable result or that a skilled artisan, looking at the prior art, would have reasonably expected success with the formulation in claim 8. Defendants' clearest statement, and the statement best supported by the evidence, is: "Formulation III of Bahal '154 (a naloxone solution with pH 3.2 and EDTA) was disclosed as being stable and would have suggested to a POSA at the very least that methylnaltrexone could also be formulated as a stable solution with a pH of 3.2 and EDTA." (Defs.' Opp. Br. 27.) This has evidentiary support but it does not, however, get Defendants where they need to go: it does not say that Bahal '154 would have suggested to a skilled artisan that methylnaltrexone could be formulated as a solution with 24-month stability with a pH of 3-4 without added stabilizers. Rather, as Plaintiffs contend in their

[8] If claim 8 taught that 24-month stability of methylnaltrexone solutions could be accomplished through the use of sodium edetate, Defendants might have a good point here.

reply brief, Bahal '154 can be read as contrary to Defendants' case. Bahal '154 reports on three naloxone formulations, all of which were prepared with a pH of 3.2. Bahal '154, col.3 ll.7-47. Formula I was the naloxone saline solution at pH 3.2, with nothing else added. Id. at col.3 ll.7-17. Formula II was the naloxone saline solution at pH 3.2, with parabens added. Id. at col.3 ll.20-33. Formula III was the naloxone saline solution at pH 3.2, with sodium edetate added. Id. at col.3 ll.35-46. Stability testing showed that Formula III was stable and Formula I showed substantial degradation. Id. at col.4 ll.43-53. This appears to teach that naloxone saline solutions at pH 3.2, without an added stabilizer, fail the stability test, and that it is the addition of sodium edetate that accounts for the improvement in stability.[9]

Defendants have not persuaded the Court that Dr. Khan's statements about Bahal '154 are supported by the evidence. Rather, they are "conclusory statements [which] do not raise any genuine issues of material fact." PC Connector Sols. LLC v. SmartDisk Corp., 406 F.3d 1359, 1364 (Fed. Cir. 2005). As the Federal Circuit has stated:

> Rather, the expert's testimony on obviousness was essentially a conclusory statement that a person of ordinary skill in the art would have known . . . how to combine any of a number of references to achieve the claimed inventions. This is not sufficient and is fraught with hindsight bias.

ActiveVideo Networks, Inc. v. Verizon Communs., Inc., 694 F.3d 1312, 1327 (Fed. Cir. 2012). That is true of Dr. Khan's cited testimony, as well.

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[9] Dr. Hunter, Defendants' chemistry expert, supported this inference in his deposition testimony:

> Q: But does Bahal ever attribute the stabilization of naloxone to the adjustment of pH to 3.2?
> A: Bahal is silent on the effect of pH on the stability of naloxone.

(Deni Dec. Ex. 24 at 73:18 - 74:1.)

The heart of Defendants' obviousness case – and the major point on which they fail – is their argument that a pH range of 3 to 4 would have been obvious to try. The legal test this Court applies centers on the crucial question of "whether the invention is an 'identified, predictable solution' and an 'anticipated success.'" Rolls-Royce, 603 F.3d at 1339. The bottom line is that Defendants have pointed to no evidence that claim 8 was either an 'identified, predictable solution' or an 'anticipated success.'

Defendants have offered no evidence to support their assertion that "[a]rriving at a pH of 3.0 to 4.0 (acidic) for the long-term stability of a methylnaltrexone solution was a predictable result." Defendants have failed to point to evidence from which a factfinder could conclude that a skilled artisan, before the critical date, would have identified claim 8 as a solution to the problem of formulating a methylnaltrexone injectable solution with 24-month stability, or that the skilled artisan would have predicted or anticipated the success of a formulation using only a pH of 3-4 to stabilize such a solution. Rather, there is nothing in the evidence of record that suggests that the art knew at all about the potential for a pH of 3-4, without added stabilizers, to be associated with 24-month stability in an injectable pharmaceutical solution. Indeed, conspicuous by its absence from the record is any prior art which discloses the idea which Defendants contend is obvious: that a pH of 3-4, without added stabilizers, results in 24-month stability in an injectable pharmaceutical solution. The prior art of record, on the whole, suggests that the prior art considered pH to be generally important in formulating pharmaceuticals, and to have an effect on stability, but the art was also pursuing the use of chemical additives, such as stabilizers or chelating agents, to improve stability of these compounds in injectable forms. Defendants have pointed to no evidence that indicates that anyone in the prior art had contemplated an injectable pharmaceutical solution made

stable over the long term by pH alone – or anything approximating that. Nor is there any evidence that the prior art had any knowledge about storage stability or degradation issues for methylnaltrexone.[10]

The evidence of record, viewed in the light most favorable to the non-movants, supports the inference that, at the time of the invention, the skilled artisan would have expected that the stability of methylnaltrexone solutions might be improved both by making the pH acidic, and by optimizing that acidic pH for peak stability. That does not provide a sufficient factual basis for a finding that, to the skilled artisan, the invention of claim 8 would have been a predictable result. There is still a substantial logical gap between that knowledge and the discovery that methylnaltrexone solutions are stable for 24 months when the pH is adjusted to the range of 3 to 4 without the use of other stabilizers. Defendants have pointed to no evidence that supports the inference that the skilled artisan had any basis to predict that that specific pH range would be associated with stability of that duration. Defendants' evidence, at best, says only that the skilled artisan, faced with the problem of developing a methylnaltrexone solution with a long shelf-life, would have expected that experimenting with acid pH might be one of a number of good places to start looking. Defendants have not shown more than that optimizing pH was a promising area for experimentation, along with others, such as the use of stabilizers, antioxidants, chelating agents, container closure system, and preservatives. This does not provide a basis to find that the invention of claim 8 was either an 'identified, predictable solution' or an 'anticipated success.' Defendants' evidence has raised no material factual disputes underlying the legal conclusion of

[10] The specification of the '025 patent states: "It was surprisingly discovered that pH alone can solve the problem of excessive methylnaltrexone degradation products." '025 patent, col.8 ll.47-49. Defendants have not cited any evidence that undermines this assertion.

nonobviousness. Plaintiffs have shown that they are entitled to Judgment as a matter of law.

The Federal Circuit has stated: "This court and obviousness law in general recognizes an important distinction between combining known options into 'a finite number of identified, predictable solutions,' *KSR*, 550 U.S. at 421, and 'merely throwing metaphorical darts at a board in hopes of arriving at a successful result." Leo Pharm. Prods. v. Rea, 726 F.3d 1346, 1357 (Fed. Cir. 2013). Continuing this metaphor, for claim 8, Defendants have shown only that the skilled artisan would have recognized adjusting pH as one dart among a number of others. Or, expressing these ideas without metaphor:

> First, an invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious. *O'Farrell*, 853 F.2d at 903. This is another way to express the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. 550 U.S. at 421. . . Second, an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *O'Farrell*, 853 F.2d at 903. This expresses the same idea as the *KSR* requirement that the identified solutions be "predictable." 550 U.S. at 421.

Bayer Schering Pharma AG v. Barr Labs., Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009). This quote expresses well the reasons why Defendants have failed to defeat Plaintiffs' motion for partial summary judgment. Defendants' evidence indicates that the skilled artisan, seeking to develop a methylnaltrexone injectable solution with long-term stability, "would have had to try all possibilities in a field unreduced by direction of the prior art." (Id.)

The motion for partial summary judgment will be granted and, as to Defendants'

affirmative defense to infringement of claim 8 of invalidity due to obviousness, Judgment will be entered in Plaintiffs' favor.

For these reasons,

IT IS on this 1st day of May, 2018,

ORDERED that Plaintiffs' motion for partial summary judgment (Docket Entry No. 197) is **GRANTED**, and, as to Defendants' affirmative defense to infringement of claim 8 of invalidity due to obviousness, Judgment is hereby entered in Plaintiffs' favor.

s/ Stanley R. Chesler
Stanley R. Chesler, U.S.D.J.