IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD., and LTS LOHMANN THERAPIE-SYSTEME AG, Plaintiffs; v. NOVEN PHARMACEUTICALS, INC., Defendant.	Civil Action No. 13-527-RGA Civil Action No. 14-111-RGA (Consolidated)

TRIAL OPINION

Michael P. Kelly, Esq., Daniel M. Silver, Esq., MCCARTER & ENGLISH, LLP, Wilmington, DE; Nicholas N. Kallas, Esq., Charlotte Jacobsen, Esq., Dominick A. Conde, Esq., Christopher E. Loh, Esq., Daniel J. Minion, Esq., FITZPATRICK, CELLA, HARPER & SCINTO, New York, NY.

Attorneys for Plaintiffs Novartis Pharmaceuticals Corp., et al.

John C. Phillips, Jr., Esq., Megan C. Haney, Esq., PHILLIPS, GOLDMAN & SPENCE, P.A., Wilmington, DE; Steven J. Lee, Esq., Michael K. Levy, Esq., Christopher J. Coulson, Esq., KENYON & KENYON LLP, New York, NY.

Attorneys for Defendant Noven Pharmaceuticals, Inc.

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ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd., and LTS Lohmann Therapie-Systeme AG (collectively, "Novartis") brought this suit against Defendant Noven Pharmaceuticals, Inc., alleging infringement of U.S. Patent Nos. 6,335,031 ("the '031 patent") and 6,316,023 ("the '023 patent"). (D.I. 1).[1] The '023 patent is no longer at issue. (D.I. 137). The parties stipulated that Noven's ANDA products infringe claims 7 and 16 of the '031 patent. (D.I. 146). Noven argues, however, that the asserted claims are invalid as obvious under 35 U.S.C. § 103(a) and invalid under obviousness-type double patenting. The Court held a three day bench trial beginning on December 1, 2014 on the issue of validity. (D.I. 154, 155 & 156). The parties filed post-trial briefing (D.I. 161, 168 & 170) and proposed statements of fact. (D.I. 162, 169 & 171).[2] For the reasons stated below, I find that Noven failed to prove by clear and convincing evidence that the asserted claims are invalid as obvious. I also find that the asserted claims are not invalid under obviousness-type double patenting.

I. BACKGROUND

Claims 7 and 16 of the '031 patent depend on non-asserted independent claims 1 and 15, which are drawn to a pharmaceutical composition and a stabilization method, respectively. Claim 1 of the '031 patent recites:

> A pharmaceutical composition comprising:

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[1] Civil Action Nos. 13-527 and 14-111 were consolidated on April 11, 2014. (D.I. 112). All docket citations in the present opinion are to Civil Action No. 13-527, unless otherwise indicated.

[2] Novartis submitted a notice of subsequent authority on May 26, 2015 (D.I. 174), informing the Court of the Federal Circuit's recent decision in *Novartis Pharm. Corp. v. Watson Labs., Inc.*, 2015 WL 2403308 (Fed. Cir. May 21, 2015), which affirmed my decision in *Novartis Pharm. Corp. v. Par Pharm., Inc.* ("*Watson*"), 48 F. Supp. 3d 733 (D. Del. 2014). Noven responded. (D.I. 175). The Federal Circuit's *Watson* decision does not control because Noven has presented additional evidence that was not before the Court in *Watson*.

> (a) a therapeutically effective amount of (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A);
>
> (b) about 0.01 to about 0.5 percent by weight of an antioxidant, based on the weight of the composition, and
>
> (c) a diluent or carrier.

(D.I. 1-1 at 6, col. 8:14–21). In the claim language "Compound A" refers to rivastigmine, the "S" enantiomer of the racemic compound RA_7.[3] Claim 7 recites a "transdermal device comprising a pharmaceutical composition as defined in claim 1, wherein the pharmaceutical composition is supported by a substrate." (*Id.*, col. 8:49–51). Claim 15 recites:

> A method of stabilizing (S)-N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate in free base or acid addition salt form (Compound A), wherein the method comprises forming a composition by combining Compound A with an amount of antioxidant effective to stabilize Compound A from degradation.

(*Id.* at 7, col. 9:10–15). Claim 16 limits the method's antioxidant to "tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate." (*Id.*, col. 10:1–3).

II. LEGAL STANDARD

A. Obviousness

The presumption that all patents are valid is the starting point for any obviousness determination. 35 U.S.C. § 282 (2012). A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." *Id.* § 103(a); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007).

[3] N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate, abbreviated as "RA_7," is a racemate. A racemate is a compound that is composed of two enantiomers of a chiral molecule, denoted as "S" and "R." The two enantiomers are identical in all respects except for the fact that they are mirror images of each other.

Obviousness is a question of law that depends on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the relevant art; and (4) any objective considerations such as commercial success, long felt but unsolved need, and the failure of others. *See KSR*, 550 U.S. at 406; *see also Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1347 (Fed. Cir. 2012). The improvement over prior art must be "more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417.

To prove obviousness, a party must show that a person having ordinary skill in the art (PHOSITA) would be motivated to combine the claimed combinations with a reasonable expectation of success. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013). Evidence of obviousness, especially when that evidence is proffered in support of an "obvious-to-try" theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were "finite," "small," or "easily traversed," and "that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012). Obviousness must be proven by clear and convincing evidence. *Id.* at 1078.

B. Obviousness-type Double Patenting

"Obviousness-type double patenting is a judicially-created doctrine designed to prevent claims in separate applications or patents that do not recite the 'same' invention, but nonetheless claim inventions so alike that granting both exclusive rights would effectively extend the life of patent protection." *In re Hubbell*, 709 F.3d 1140, 1145 (Fed. Cir. 2013) (internal quotation

marks omitted).[4] Under this doctrine, the court must determine "whether the claimed invention in the application for the second patent would have been obvious from the subject matter of the claims in the first patent, in light of the prior art." *In re Longi*, 759 F.2d 887, 893 (Fed. Cir. 1985). In order to do so, the court applies a two-step analysis: "First, the court construes the claim[s] in the earlier patent and the claim[s] in the later patent and determines the differences. Second, the court determines whether those differences render the claims patentably distinct." *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1374 (Fed. Cir. 2014) (internal quotation marks omitted). "A later claim that is not patentably distinct from . . . an earlier claim is invalid for obviousness-type double patenting." *Id.* (internal quotation marks omitted).

III. FINDINGS OF FACT

1. The PHOSITA is an individual, or team of individuals, with an advanced degree in chemistry, pharmacy, or a related field with at least two years of practical experience, or a master's or bachelor's degree in those disciplines and at least four or six years of practical experience, respectively.

2. The following are all prior art references: Sasaki (DTX 12); Carey & Sundberg (DTX 32); Ansel (DTX 91); *Modern Pharmaceutics* (PTX 153); *Physician's Desk Reference* (PTX 157); *Remington's Pharmaceutical Sciences* (JTX 5); *Handbook of Pharmaceutical Excipients* (JTX 8); the '480 patent (JTX 9); Sramek (JTX 11); the '807 patent (JTX 17); GB '040 (JTX 19); the '176 patent (JTX 20); Elmalem (JTX 21); Formulary (JTX 25); Ebert (JTX 28); Weinstock 1981 (JTX 30); Linnell (JTX 32); Weinstock 1994 (PTX 175); and Enz 1991 (PTX 174).

3. A PHOSITA would not have known rivastigmine was susceptible to oxidative degradation based on its chemical structure.

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[4] The Federal Circuit has recognized three major distinctions between obviousness under 35 U.S.C. § 103 and nonstatutory (obviousness-type) double patenting:

> (1) The objects of comparison are very different: Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application; (2) Obviousness requires inquiry into a motivation to modify the prior art; nonstatutory double patenting does not; (3) Obviousness requires inquiry into objective criteria suggesting non-obviousness; nonstatutory double patenting does not.

Geneva Pharm., Inc. v. GlaxoSmithKline PLC, 349 F.3d 1373, 1377–78 n.1 (Fed. Cir. 2003).

4. Comparing rivastigmine to nicotine would not have informed a PHOSITA that rivastigmine was susceptible to oxidative degradation.

5. None of the prior art references teach a PHOSITA that rivastigmine is susceptible to oxidative degradation.

6. Rivastigmine was not known to be susceptible to oxidative degradation.

7. It would not have been obvious to a PHOSITA to combine an antioxidant with rivastigmine in a transdermal patch.

IV. CONCLUSIONS OF LAW

A. Obviousness

Noven argues that claims 7 and 16 of the '031 patent are invalid for obviousness. In a previous case involving the '031 and '023 patents, where claims 7 and 16 of the '031 patent were at issue, I stated that:

> [T]he obviousness determination in this case turns on whether a PHOSITA in January 1998, looking at all of the prior art, would have known rivastigmine was susceptible to oxidative degradation. If the answer is yes, the asserted claims of the '023 and '031 patents are invalid because the addition of an antioxidant to a pharmaceutical composition that oxidatively degrades is one of several known, obvious solutions. If the answer is no, then the discovery that rivastigmine oxidatively degrades and the solution to that problem are an inventive contribution worthy of patent protection.

Novartis Pharm. Corp. v. Par Pharm., Inc. ("*Watson*"), 48 F. Supp. 3d 733, 758 (D. Del. 2014), *aff'd sub nom.*, *Novartis Pharm. Corp. v. Watson Labs., Inc.*, 2015 WL 2403308 (Fed. Cir. May 21, 2015) (internal citations omitted).[5] Noven has introduced new evidence that was not before

[5] In the prior decision, I found that "a PHOSITA would not have appreciated rivastigmine's susceptibility to oxidative degradation in January 1998," and thus held that defendant failed to prove obviousness by clear and convincing evidence. *See Watson*, 48 F. Supp. 3d at 758. The Federal Circuit affirmed that decision on appeal. *See Watson*, 2015 WL 2403308, at *8. Familiarity with both decisions is presumed.

the Court in *Watson*. Nevertheless, my analysis reaches the same conclusion as in the prior case.

1. Chemical Structure

Noven argues that a PHOSITA in 1998 would have examined the chemical structure of rivastigmine and recognized that it is susceptible to oxidative degradation. (D.I. 161 at 8). Noven cites the Ansel reference, which states that "one of the most important activities of preformulation work is the evaluation of the physical and chemical stability of the pure drug substance." (DTX 91 at 91 [Howard C. Ansel, *Introduction to Pharmaceutical Dosage Forms* 91 (4th ed. 1985)]). Ansel further states, "Initial investigation begins through knowledge of the drug's chemical structure which allows the preformulation scientist to anticipate the possible degradation reactions." (*Id.*). Noven's expert, Dr. Schöneich, identified a carbon-hydrogen bond in rivastigmine that is "particularly susceptible" to oxidation because the bond is "immediately adjacent" to: (1) an "aromatic ring"; (2) a "tertiary amine"; and (3) an "additional carbon substituent," making the carbon in the carbon-hydrogen bond a "tertiary carbon." (Trial Tr. at 48:2–49:13 & 60:22–61:6).[6]

Dr. Schöneich relied on the Carey & Sundberg reference, published in 1990, which explains, "The radical stabilization provided by various functional groups results in reduced bond dissociation energies for bonds to the stabilized radical center." (*Id.* at 63:16–67:23; DTX 32 at p. 683 [Francis A. Carey & Richard J. Sundberg, *Advanced Organic Chemistry* 683 (3d ed. 1990)]). The book states that "[s]ubstrates that are relatively electron-rich or that provide particularly stable radicals are the most easily oxidized," noting that "[b]enzylic, allylic, and

[6] The official transcript of the bench trial is broken up into three docket numbers (D.I. 154, 155 & 156), but all citations to the transcript are cited as "Trial Tr."

tertiary positions are especially susceptible to oxidation." (DTX 32 at p. 693). Dr. Schöneich explained that "[w]hen the carbon hydrogen bond is broken in any organic molecule . . . the organic molecule has become oxidized," resulting in the formation of "radicals," which "could undergo further reactions and ultimately convert into a different chemical entity." (Trial Tr. at 56:23–57:7). Dr. Schöneich concluded that a PHOSITA would reasonably expect rivastigmine to be susceptible to oxidation because of its weak carbon-hydrogen bond. (*Id.* at 75:6–76:10).

Novartis, on the other hand, asserts that Noven's structural argument relies on rivastigmine's "theoretical susceptibility" to oxidative degradation. (D.I. 168 at 17). Novartis's expert, Dr. Klibanov, admitted that certain groups of atoms were known to "potentially" undergo oxidative degradation in pharmaceutical formulations in 1998. (Trial Tr. at 421:20–422:8). He made clear that the presence of these functional groups would lead a PHOSITA to conclude "that there is a potential for such a degradation to take place, which may or may not take place depending on the rest of the molecule and experimental conditions, but the ultimate determination can only be done by testing." (*Id.* at 423:11–424:5). Novartis cites the Connors reference, published in 1986, which states that "many molecules tend to be converted to a more oxidized state" when exposed to oxygen, but "[k]inetically . . . there is a sufficient energy barrier to many such reactions (the energy of activation) that not all molecules are subject to measurable rates of spontaneous oxidation or autoxidation." (JTX 22 at 82 [Kenneth A. Connors et al., *Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists* 82 (2d ed. 1986)]).

Novartis points out that Noven's expert, Dr. Kydonieus, conceded that merely knowing that a compound is susceptible to oxidation "doesn't tell you how much degradation you will get period depending on that formulation." (Trial Tr. at 232:6–13). Dr. Schöneich stated, "[I]f

you have a drug which is susceptible to degradation, the extent to which it actually happens, that depends on the environment." (*Id.* at 96:4–7). Dr. Schöneich admitted that he did not know "whether rivastigmine is susceptible to oxidative degradation in pharmaceutical compositions," and that "whether it actually degrades and at which rate, that depends on how the formulation is made up." (*Id.* at 94:21–95:13).

Novartis cites the *Modern Pharmaceutics* reference, which states, "Through the application of functional group chemistry, it is possible to anticipate the potential mode(s) of degradation that drug molecules will likely undergo." (PTX 153 at 181 [*Modern Pharmaceutics* 181 (Gilbert S. Banker & Christopher T. Rhodes eds., 3d ed. 1996)]). Novartis highlights, however, that the book acknowledges that "[i]t is not the intent of this chapter to document stability data of various individual drugs," directing readers to "compilations of stability data" and "literature on specific drugs . . . for this kind of information." (*Id.* at 180). Novartis also points out that *Modern Pharmaceutics* does not disclose benzylic carbon-hydrogen bonds or amines, which Noven identified in rivastigmine as causing potential for oxidative degradation. (*Id.* at 183). Dr. Schöneich admitted that he did not review any data regarding rivastigmine's susceptibility to oxidative degradation in a transdermal formulation, and that he was unaware of any prior art that provided stability testing for rivastigmine formulations. (Trial Tr. at 95:7–23). Dr. Kydonieus also admitted that "none of the prior art references that [he] cited provided any stability data on rivastigmine or RA_7 formulations." (*Id.* at 233:5–11).

Novartis asserts that a PHOSITA would have known that the structure of a compound as a whole determines the compound's stability. (D.I. 168 at 20). Dr. Klibanov explained that "one of the basic principles in chemistry is that the structure of a molecule as a whole . . . affects the properties of this molecule, including oxidative degradation," and that "one of skill in the art

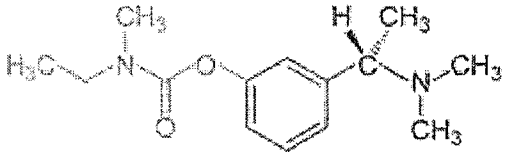
would understand that simply zeroing in on the particular segment of the molecule and ignoring the rest of the molecule is not the way to analyze it." (Trial Tr. at 316:2–17). Dr. Klibanov used physostigmine as an example, explaining that the "tertiary amines, even though they're located on the opposite side of the physostigmine molecule, nonetheless affect the hydrolysis of this carbamate." (*Id.* at 424:6–425:23). Dr. Klibanov concluded that a PHOSITA would understand that this "confirms the basic notion . . . that [it is] the structure of the molecule as a whole, not just the particular presence of a particular group, that affects the stability of the molecule, including its oxidative degradation stability or instability." (*Id.* at 425:11–23). Dr. Klibanov also used dextromethorphan as an example (*Id.* at 443:14–444:14), which Dr. Schöneich had originally used in his expert report to support his chemical structure theory. (*Id.* at 103:3–11). Dr. Klibanov explained that dextromethorphan has a benzylic carbon-hydrogen bond, but was reported to be a "very stable drug substance" and to have "excellent stability" under pharmaceutically relevant conditions. (*Id.* at 443:14–444:14; JTX 24 at 433; PTX 180 at 621–22). Thus, Novartis argues that the presence of certain functional groups in rivastigmine would not tell a PHOSITA anything about its actual susceptibility to oxidative degradation.

While the prior art teaches that certain functional groups may allow a PHOSITA to "anticipate the possible degradation reactions," both parties' experts agree that actual testing is necessary to determine what—if any—degradation actually occurs. Noven's experts admitted that no studies were conducted with respect to rivastigmine's actual chemical stability prior to January 1998. If a PHOSITA would have known that rivastigmine was susceptible to oxidative degradation by looking at its chemical structure, then the problem would have been identified in the prior art soon after rivastigmine's structure was disclosed. This, however, did not occur. The chemical structure of rivastigmine was known ten years prior to January 1998, but the first

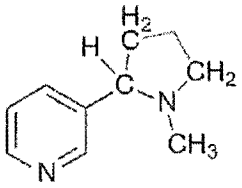
mention of its susceptibility to oxidative degradation appears in the '031 patent. Thus, I conclude a PHOSITA would not have known that rivastigmine was susceptible to oxidative degradation based on its chemical structure alone.

2. Nicotine Comparison

Below are the chemical structures of rivastigmine and nicotine, as provided by the parties at trial:



Rivastigmine



Nicotine

Noven argues that rivastigmine's structural similarity to nicotine, which was known to be susceptible to oxidative degradation in 1998, would have reinforced a PHOSITA's reasonable expectation that rivastigmine was susceptible to oxidation. (D.I. 161 at 10). Noven relies on two Federal Circuit cases for the proposition that a PHOSITA would understand that chemical compounds with similar structures often have similar properties. *See Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 976 (Fed. Cir. 2014) ("[S]tructurally similar compounds often have similar properties."); *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) ("[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness."). The Federal Circuit also stated that "[t]he 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in

light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Aventis*, 499 F.3d at 1301.

Noven cites the Linnell reference, published in 1960, which discloses that nicotine is susceptible to oxidative degradation. (Trial Tr. at 86:19–87:13; JTX 32 at 90–91). Noven also cites PCT Publication WO 95/24172 ("Ebert"), an international patent application filed in 1995, which states, "Another trait of nicotine that can be problematic is its tendency to oxidize readily in the presence of light and air." (Trial Tr. at 149:12–20; JTX 28 at 19:17–19). Novartis's expert, Dr. Klibanov, agreed that as of 1998 nicotine was known to undergo oxidative degradation "under some pharmaceutically relevant conditions." (Trial Tr. at 452:1–5). Dr. Schöneich explained that, like rivastigmine, nicotine contains a carbon-hydrogen bond that is immediately adjacent to an aromatic ring system, a tertiary amine, and another alkyl substituent. (*Id.* at 87:14–88:11).[7] Dr. Schöneich therefore concluded that a PHOSITA would draw conclusions about rivastigmine's susceptibility to oxidation based on the structural similarities with nicotine, stating, "[W]e have to understand these are not identical compounds, but similar enough that these conclusions can be drawn." (*Id.* at 89:11–20).

Novartis argues that a PHOSITA would not have considered nicotine and rivastigmine structurally similar. (D.I. 168 at 23). Dr. Klibanov conducted a comparative analysis of the structures of rivastigmine and nicotine, finding that a PHOSITA would conclude that the two structures "are very different." (Trial Tr. at 448:15–449:11). He found that unlike rivastigmine, nicotine does not have a carbamate moiety, a benzene ring, or a benzylic carbon-hydrogen bond, and has a pyrrolidine ring, a pyridine ring, and a tertiary amine that is part of a

[7] Dr. Schöneich noted that nicotine and rivastigmine have different aromatic rings, but stated that both rings can undergo "electron delocalization" and generate "resonance structures." (Trial Tr. at 88:12–89:10).

ring structure. (*Id.* at 448:15–451:24). Dr. Klibanov also explained that a PHOSITA "would know that the stability of a chemical molecule is determined by the entirety of its structure," and "[i]f the structures are very different, then the stabilities have to be different." (*Id.* at 451:11–24). Thus, Dr. Klibanov concluded that a PHOSITA "would not mechanically extrapolate from whatever is known about nicotine to rivastigmine." (*Id.* at 451:21–24).

Although obviousness is a question of law, it is a fact-intensive inquiry. Unlike *Bristol-Myers* and *Aventis*, where the Federal Circuit addressed claimed compounds that were slight variations over otherwise identical compounds in the prior art, rivastigmine and nicotine are different chemical compounds with different chemical structures. I am not convinced that nicotine and rivastigmine share a "sufficiently close relationship" that a PHOSITA would expect them to have "similar properties." Thus, a PHOSITA would not have been motivated to compare these two compounds. Even if a PHOSITA were motivated to compare the two compounds, I do not think their structures are sufficiently similar to make any determinations about rivastigmine's chemical stability. Therefore, a PHOSITA would not have known that rivastigmine was susceptible to oxidative degradation by comparing it to nicotine.

3. Prior Art References

Noven argues that claims 7 and 16 of the '031 patent are invalid as obvious in light of the following prior art references: UK Patent Application GB 2 203 040 A ("GB '040"), Japanese Patent Application No. JP 59-184121 ("Sasaki"), the *Handbook of Pharmaceutical Excipients* (the "*Handbook*"), Ebert, the Elmalem article, the Weinstock 1981 article, and U.S. Patent No. 4,948,807 ("the '807 patent").[8] While GB '040, the '807 patent, and Elmalem were discussed

[8] Noven also introduced Sramek (JTX 11), the Formulary article (JTX 25), *Remington's Pharmaceutical Sciences* (*Remington's*) (JTX 5), and U.S. Patent No. 5,061,480 ("the '480 patent") (JTX 9). None of these prior art

at length in my *Watson* decision, 48 F. Supp. 3d at 753–58, and addressed on appeal, 2015 WL 2403308, at *2–4, each piece of prior art must be analyzed in light of the new evidence Noven has introduced. Noven's obviousness argument also relies on the presumption that a PHOSITA would have reasonably expected that rivastigmine was susceptible to oxidative degradation based on its chemical structure and its similarity to nicotine. Having found that Noven has not proven that a PHOSITA would have known that rivastigmine was susceptible to oxidative degradation based on its chemical structure or its similarity to nicotine, I find that claims 7 and 16 are not obvious in light of the prior art.

Noven argues that a PHOSITA would have been motivated to combine the teachings of GB '040 and Sasaki to arrive at the subject matter of claims 7 and 16 of the '031 patent. As discussed in my *Watson* opinion, 48 F. Supp. 3d at 753–54, GB '040 does not disclose rivastigmine's susceptibility to oxidative degradation or the addition of an antioxidant.[9] Sasaki, which was not introduced in *Watson*, is an unexamined Japanese patent application filed in 1983 that discloses the addition of the antioxidant tocopherol to an acrylic adhesive in order to prevent a drug containing an amino group from undergoing degradation during storage. (DTX 12). Sasaki does not, however, disclose rivastigmine or its susceptibility to oxidative degradation. Noven also cites the *Handbook*, which discloses a number of excipients that can be used in pharmaceutical compositions, including the use of BHA and BHT for topical pharmaceutical applications. (JTX 8). Noven argues that the *Handbook* would have reinforced a PHOSITA's

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references, however, make any reference to rivastigmine's susceptibility to oxidative degradation or to the addition of an antioxidant to rivastigmine.

[9] Noven mentions in a footnote that Example 2 of GB '040 includes BRIJ 97, which contains BHA and citric acid, two known antioxidants. (D.I. 161 at 21 & n.7; D.I. 154 at 170:11–171:3). I find that the antioxidants in BRIJ 97 were not used to stabilize rivastigmine, and thus a PHOSITA would not have known that rivastigmine was susceptible to oxidative degradation based on Example 2 of GB '040. (D.I. 155 at 34:10–19).

reasonable expectation that rivastigmine could be paired with an antioxidant. The *Handbook*, however, does not disclose rivastigmine's susceptibility to oxidative degradation.

Noven also cites the Elmalem article, published in 1991, comparing the effects of three drugs, including RA_7 (rivastigmine racemate), to physostigmine. (JTX 21). Elmalem states, "All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation." (*Id.* at p. 1060). Dr. Kydonieus stated that this sentence would tell a PHOSITA that an antioxidant was added to all of the drugs in the experiment, including RA_7, to prevent oxidation. (Trial Tr. at 151:15–152:16). Dr. Klibanov disagreed, however, stating that sodium metabisulphite was added to physostigmine to prevent oxidation, and to all the other drugs as a control. (*Id.* at 374:20–375:9). Dr. Klibanov stated that an equal concentration of antioxidant was added to the saline solution before adding the different drugs in order to keep the number of variables constant. (*Id.* at 400:5–401:7). He explained that an antioxidant must be added to physostigmine in an aqueous solution to prevent the oxidation of physostigmine's hydrolytic degradant. (*Id.* at 379:16–381:13). Thus, Dr. Klibanov concluded that a PHOSITA would not have believed that an antioxidant was added to each drug to prevent it from oxidizing. (*Id.* at 404:7–405:4).

Noven argues that a PHOSITA's understanding of Elmalem would have been reinforced by Weinstock 1981, an article published in 1981, the authors of which included one of the authors of Elmalem. (JTX 30). The authors of the study measured the effects of morphine acting in the presence of several different drugs, including physostigmine. (Trial Tr. at 154:1–7 & 413:19–415:1). Weinstock 1981 does not disclose rivastigmine or RA_7. (*Id.* at 409:2–4). Similar to Elmalem, Weinstock 1981 states, "Morphine and physostigmine were made up freshly for each experiment in sterile saline which included an equal weight of ascorbic acid to prevent

oxidation." (*Id.* at 154:8–14; JTX 30 at p. 505). Dr. Kydonieus opined that the authors of Weinstock 1981 only used an antioxidant for morphine and physostigmine because they knew they were the only two drugs that needed an antioxidant. (Trial Tr. at 154:15–155:3). Thus, he concluded that a PHOSITA would have known that the authors of Elmalem added an antioxidant to RA_7 because they knew it was susceptible to oxidative degradation. (*Id.* at 156:5–16).

Dr. Klibanov, on the other hand, stated that Weinstock 1981 involved a different experiment and purpose than those of Elmalem. (*Id.* at 409:2–410:9). He explained that the purpose of the Weinstock 1981 study was to determine whether the effects of morphine were exerted through the central or peripheral nervous system. (*Id.* at 410:19–412:13; JTX 30 at p. 504). The results of the Weinstock 1981 study were qualitative, rather than quantitative. (Trial Tr. at 415:23–416:17). Dr. Klibanov highlighted that Elmalem was intended to be a head-to-head comparison of the physiological effects of different drugs to those of physostigmine. (*Id.* at 395:21–396:24). He explained that the authors of Elmalem had to control for the antioxidant required by physostigmine to compare the relative efficacies of the other drugs. I find Dr. Klibanov's testimony regarding Elmalem to be more credible than that of Noven's expert. I also find that Weinstock 1981 would not change a PHOSITA's reading of Elmalem. Thus, I accept Novartis's position, and find that neither Elmalem nor Weinstock 1981 discloses rivastigmine's susceptibility to oxidative degradation.

Finally, Noven cites the '807 patent, which issued in 1990 and included two of the authors from Elmalem and one from Weinstock 1981. (JTX 17). As discussed in *Watson*, 48 F. Supp. 3d at 754–55, the '807 patent teaches that sterile injectable formulations of the claimed compounds, including RA_7, can incorporate an antioxidant. The '807 patent states that for the

sterile compositions "[b]uffers, preservatives, antioxidants and the like can be incorporated as required," and that "[p]referred antioxidants for use with the compounds of the present invention include sodium metabisulphite and ascorbic acid." (JTX 17 at 7:45–53). As I noted in *Watson*, 48 F. Supp. 3d at 754, however, the '807 patent does not suggest that RA_7 requires an antioxidant or that it undergoes oxidative degradation.[10] The only reference the '807 patent makes to stability suggests that RA_7 and the other claimed compounds are more stable than physostigmine. Therefore, the '807 patent does not disclose rivastigmine's susceptibility to oxidative degradation.

Novartis argues that none of the prior art references cited by Noven disclose rivastigmine's susceptibility to oxidative degradation, and that the only references that mention its stability refer to it having greater stability than physostigmine. Novartis cites the Weinstock 1994 article, published by some of the authors of Elmalem and some of the inventors of the '807 patent. Weinstock 1994 states that rivastigmine "showed superior chemical stability" to physostigmine. (PTX 175 at 219; Trial Tr. at 406:21–408:21). Novartis also highlights the Enz 1991 article, written by the inventor of GB '040, which states that rivastigmine "appears to have greater chemical stability" than physostigmine. (PTX 174 at 272; Trial Tr. at 406:21–408:21).

Novartis also relies on the Federal Circuit's decision in *Leo Pharm. Prods., Ltd. v. Rea*, finding that the inventors of the claimed invention "recognized and solved a problem with the storage stability of certain formulations—a problem that the prior art did not recognize and a problem that was not solved for over a decade." 726 F.3d 1346, 1353 (Fed. Cir. 2013). In

[10] I also noted in *Watson* that the patent examiner for the '023 and '031 patents considered both the '807 patent and the '176 patent (the US equivalent of GB '040) during prosecution. *Watson*, 48 F. Supp. 3d at 755.

Leo, the Federal Circuit noted that "[t]he ordinary artisan would first have needed to recognize the problem, i.e., that the formulations disclosed in [the prior patents] were not storage stable," and "[t]o discover this problem, the ordinary artisan would have needed to spend several months running storage stability tests." *Id.* at 1354. The Federal Circuit explained that "[o]nly after recognizing the existence of the problem would an artisan then turn to the prior art and attempt to develop a new formulation for storage stability," and "[i]f these discoveries and advances were routine and relatively easy, the record would undoubtedly have shown that some ordinary artisan would have achieved this invention within months of [the two prior patents]," instead of "more than a decade" later. *Id.*

I agree with Novartis that none of the prior art references cited by Noven disclose rivastigmine's susceptibility to oxidative degradation. I say this in light of finding that a PHOSITA would not have known rivastigmine was susceptible to oxidative degradation based on its chemical structure or its similarity to nicotine. Like the claimed compound in *Leo*, rivastigmine's structure had been known for at least ten years prior to January 1998, and no prior art references mention its susceptibility to oxidative degradation. If this discovery were routine, then it would have appeared in the prior art. Instead, it remained undiscovered for a decade. Therefore, a PHOSITA would not have known that rivastigmine was susceptible to oxidative degradation based on the prior art.

4. Conclusion

In sum, a PHOSITA would not have known rivastigmine was susceptible to oxidative degradation in 1998 based on its chemical structure or its similarity to nicotine, and none of the prior art references disclose rivastigmine's susceptibility to oxidative degradation. Thus, a PHOSITA would not have known rivastigmine was susceptible to oxidative degradation in

January 1998. Therefore, Noven has failed to prove by clear and convincing evidence that claims 7 and 16 of the '031 patent are invalid as obvious.

B. Obviousness-type Double Patenting

Noven asserts that claims 1, 3, 8, and 11 of U.S. Patent No. 5,602,176 ("the '176 patent") (JTX 20) render claims 7 and 16 of the '031 patent invalid under obviousness-type double patenting. (D.I. 161 at 32). The '176 patent is the U.S. equivalent of GB '040. The '031 patent is jointly owned by Novartis AG and LTS, and the '176 patent is solely owned by Novartis AG. (D.I. 162 & 169 ¶¶ 225–28). Noven argues that the '176 patent and '031 patent are "commonly owned" for purposes of double patenting because they share Novartis AG as a common assignee. (D.I. 161 at 30). Noven concedes that the antioxidant element of claims 7 and 16 of the '031 patent is not present in the claims of the '176 patent. (*Id.* at 33). Noven argues, however, that this was an obvious improvement. I find that the prior art, including GB '040 and the '176 patent, does not disclose rivastigmine's susceptibility to oxidative degradation. Thus, the addition of an antioxidant makes claims 7 and 16 of the '031 patent "patentably distinct" from claims 1, 3, 8, and 11 of the '176 patent. Therefore, claims 7 and 16 of the '031 patent are not invalid under obviousness-type double patenting.

Alternatively, obviousness-type double patenting fails as a matter of law because the '176 patent and '031 patent were not filed by the same inventive entity, have no inventors in common, and are not entirely owned by the same entity. In *Hubbell*, the Federal Circuit noted that "the MPEP [Manual of Patent Examining Procedure] provides that obviousness-type double patenting may exist between an issued patent and an application filed by 'the same inventive entity, or by a different inventive entity having a common inventor, and/or by a common assignee/owner.'" *In re Hubbell*, 709 F.3d at 1146–48 (citing MPEP § 804). The Federal Circuit further stated that

"the MPEP standard is consistent with the rationale we have used to support application of obviousness-type double patenting rejections." *Id.* Novartis notes that MPEP § 706.02(l) defines "common ownership" as "entirely or wholly owned by the same person(s) or organization(s)." The '176 patent was invented by Albert Enz, and does not share any inventors with the '031 patent. (JTX 20; D.I. 1-1). Thus, the two patents were not filed by "the same inventive entity" and do not share "a common inventor." Further, the two patents are not "entirely or wholly owned by the same person(s) or organization(s)." Thus, the common ownership requirement is not met. Therefore, obviousness-type double patenting does not apply.

V. CONCLUSION

Noven has failed to prove by clear and convincing evidence that claims 7 and 16 of the '031 patent are invalid as obvious. Further, the asserted claims are not invalid under obviousness-type double patenting. Novartis should submit an agreed upon form of final judgment within two weeks.