

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.

PAR PHARMACEUTICAL, INC.,

Defendant.

Civil Action No. 11-1077-RGA  
(Consolidated)

NOVARTIS PHARMACEUTICALS  
CORPORATION, NOVARTIS AG,  
NOVARTIS PHARMA AG, NOVARTIS  
INTERNATIONAL PHARMACEUTICAL  
LTD., and LTS LOHMANN THERAPIE-  
SYSTEME AG,

Plaintiffs,

v.

WATSON LABORATORIES, INC.,  
WATSON PHARMA, INC., and ACTAVIS,  
INC.,

Defendants.

Civil Action No. 11-1112-RGA

TRIAL OPINION

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June 18, 2014

  
ANDREWS, U.S. DISTRICT JUDGE:

Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd., and LTS Lohmann Therapie-Systeme AG (collectively, “Novartis” or “Plaintiff”) brought this suit against Watson Laboratories, Inc., Watson Pharma, Inc., Watson Pharmaceuticals, Inc. (collectively “Watson” or “Defendant”), and Par Pharmaceutical, Inc.<sup>1</sup> alleging infringement of U.S. Patent Nos. 6,335,031 (“the ’031 patent”) and 6,316,023 (“the ’023 patent”) (collectively, “the patents in suit”). Both patents share the same specification.<sup>2</sup> The ’031 and ’023 patents claim pharmaceutical compositions, transdermal devices, and methods of stabilizing compositions comprising the drug rivastigmine, which is an acetylcholinesterase inhibitor, and an antioxidant. (D.I. 310, p. 1). Novartis sells an Exelon<sup>®</sup> transdermal patch for the treatment of Alzheimer’s disease that contains rivastigmine. Novartis listed the ’031 and ’023 patents in the Food and Drug Administration’s “Approved Drug Products with Therapeutic Equivalence Evaluations,” frequently referred to as the “Orange Book,” as covering the Exelon<sup>®</sup> patches. Watson’s Abbreviated New Drug Application 202,119 (“ANDA”) seeks approval to engage in the commercial manufacture, importation, use, or sale of a transdermal patch containing rivastigmine and an antioxidant prior to the expiration of the patents in suit.

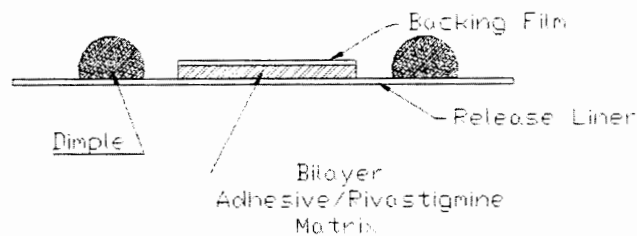
Watson’s ANDA product is a transdermal patch that contains a backing film, an adhesive bilayer comprised of a 905A adhesive and a 900A adhesive, and a protective release liner, a schematic of which is shown below:

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<sup>1</sup> Both the Par and Watson defendants were scheduled for trial beginning on August 26, 2013. Par and Novartis informed the Court on the morning of the first day of trial that a settlement had been reached. Relying on this representation, the Court entered an order staying the action with respect to Par for forty-five days and dismissed Par from the trial. (D.I. 293). The settlement later fell through, and a trial for Par and Novartis took place on May 1, 2014.

<sup>2</sup> Unless otherwise noted, all citations to the specification refer to the ’031 patent.

## Side View



(JTX 56, p. 1822-23). The process for manufacturing Watson's ANDA product can be summarized as follows: 1) the 905A adhesive and rivastigmine, the active ingredient, are mixed to form the 905A casting solution; 2) the 905A casting solution is applied to a polyester release liner, which is subsequently passed through a drying oven; 3) the 900A adhesive is applied to a polyester release liner and passed through a drying oven; 4) the release liner for the 905A layer is removed and the exposed 905A layer is laminated onto the 900A layer, thereby forming the adhesive bilayer; 5) the adhesive bilayer is then cut to size, packaged, and heat sealed into pouches. (*Id.*, pp. 1832-34). Watson's ANDA product is available in 5 and 10 square centimeter sizes. (*Id.*).

Novartis asserts that Watson's ANDA products infringe claims 3, 7, 13, 16, and 18 of the '031 patent and claims 2 and 7 of the '023 patent. Watson counters that the asserted claims are obvious under 35 U.S.C. § 103(a) and not infringed. The Court held a four day bench trial from August 26-29, 2013. (D.I. 306, 307, 308 & 309). As explained below, Novartis proved that Watson's ANDA products infringe by a preponderance of the evidence, and Watson did not prove by clear and convincing evidence that the asserted claims were invalid as obvious.

## I. INFRINGEMENT

The five asserted claims in the '031 patent depend from non-asserted independent claims 1, 11, and 15, which are drawn to pharmaceutical compositions, transdermal devices, and a stabilization method, respectively. Claim 1 of the '031 patent recites:

A pharmaceutical composition comprising:

- (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.

'031 patent, claim 1. In the claim language "Compound A" refers to rivastigmine, the "S" enantiomer of the racemic compound RA<sub>7</sub>.<sup>3</sup> Claim 3 narrows the pharmaceutical composition to those in which the antioxidant is "tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate." Claim 7 recites a "transdermal device comprising a pharmaceutical composition as defined in claim 1, wherein the pharmaceutical composition is supported by a substrate."

The requirements of claim 11 are as follows:

A transdermal device comprising a backing layer, a layer comprising a therapeutically effective amount of (S)-N-ethyl-3-{{(1-dimethylamino)ethyl}}-N-methyl-phenyl-carbamate (Compound A) and an amount of antioxidant effective to stabilize Compound A from degradation in a polymer matrix, a release-liner and, disposed between the layer comprising Compound A in a polymer matrix and the release-liner, a discrete layer of adhesive material for releasably fixing said transdermal device to a patient's skin.

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<sup>3</sup> N-ethyl-3-{{(1-dimethylamino)ethyl}}-N-methyl-phenyl-carbamate, abbreviated as "RA<sub>7</sub>," 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. (Tr. 67:17-69:1).

*Id.*, claim 11. Claim 13 limits the identity of the antioxidant in the transdermal device to “tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate.”

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.*, claim 15. Claim 16 limits the method’s antioxidant to “tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate,” and claim 18 limits the amount of antioxidant to “about 0.01 to about 0.5% by weight based on the weight of the composition.”

Two claims from the ’023 patent, claims 2 and 7, are also asserted by Novartis. Claim 2 depends from claim 1, which recites:

A pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

’023 patent, claim 1. Claim 2 limits the composition of claim 1 to those where the antioxidant is “tocopherol, esters of tocopherol, ascorbic acid, esters of ascorbic acid, butylhydroxytoluene, butylhydroxyanisole, propyl gallate, and combinations thereof.” Independent claim 7 requires:

A transdermal device comprising a pharmaceutical composition comprising 1 to 40 weight percent of (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate in the form of a free base or acid addition salt, 0.01 to 0.5 weight percent of an antioxidant, and a diluent or carrier, wherein the weight percents are based on the total weight of the pharmaceutical composition.

*Id.*, claim 7.

The claims asserted by Novartis can be broken down into two groups: the “presence” claims and the “function” claims. Claims 3 and 7 of the ’031 patent, as well as claims 2 and 7 of the ’023 patent, constitute the presence claims. These claims require proof that Compound A and an antioxidant are present. The Court defined “antioxidant” as an “agent that reduces oxidative degradation.” (D.I. 250, pp. 1-2). There is no additional requirement that the antioxidant function with respect to Compound A because that is specifically required in the function claims. (*Id.*, p. 2 (“The patents repeatedly disclose the combination of Compound A and the antioxidant without specifically requiring that the antioxidant affect Compound A. It would be improper to preclude those embodiments by limiting ‘antioxidant’ to require that interaction.” (internal citations omitted))).

Claims 13, 16, and 18 of the ’031 patent are referred to as the function claims. All three claims require “an amount of antioxidant effective to stabilize compound A from degradation,” which the Court construed to mean, “an amount of antioxidant that will significantly reduce degradation of Compound A over a prolonged period of time.” (*Id.*, pp. 2-3). The function claims, therefore, have an additional requirement that the antioxidant interact with Compound A to reduce degradation. The Court also construed “stabilizing” to mean “significantly reducing degradation over a prolonged period of time.” (*Id.*, p. 3). These three terms are the only ones at issue, and the parties agree that the remaining elements of the asserted claims are met. (D.I. 310, pp. 29-30).

In its post-trial briefing, Watson contends Novartis failed to prove infringement of the presence claims because those claims have a functional limitation and Novartis never proved that Watson’s product contains an agent that reduces oxidative degradation of any component. (D.I. 318, pp. 1-2). Watson asserts it does not infringe the function claims because the testing

conducted by Novartis's experts does not prove that Watson's ANDA product is an oxidative environment or that it contains a functioning antioxidant.

### **A. 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.<sup>4</sup> *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) (citing *Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1361 (Fed. Cir. 1983)). Infringement can be shown by "any method of analysis that is probative of the fact of infringement," and, in some cases, "circumstantial evidence may be sufficient." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009).

### **B. Findings of Fact**

1. Butylhydroxytoluene ("BHT") is a well-known antioxidant.
2. BHT is present in Watson's ANDA product.
3. BHT is present in an amount between 0.01 and 0.5 percent by weight.
4. Rivastigmine is subject to oxidative degradation in an oxidative environment.
5. The presence of oxygen, peroxides, or other free radical generators creates an oxidative environment.

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<sup>4</sup> There are no assertions of infringement by the doctrine of equivalents.



6. Oxygen, peroxides, and other free radical generators are present in Watson's ANDA product.
7. Watson's ANDA products show only minimal degradation of rivastigmine over a prolonged period of time.
8. BHT acts as an antioxidant to protect rivastigmine from oxidative degradation.
9. Watson's ANDA product infringes all asserted claims of the '023 and '031 patents.

### C. Conclusions of Law

#### 1. The Presence Claims

##### a. The presence claims do not require a functioning antioxidant

The three limitations of the presence claims are: Compound A, a certain weight percent of antioxidant, and a diluent or carrier. *See, e.g.*, '031 patent, claim 1. Unlike the function claims, nowhere in the presence claims is any function of the antioxidant mentioned. *Compare id.* (requiring Compound A and “about 0.01 to about 0.5 percent by weight of an antioxidant”), *with id.*, claim 11 (reciting Compound A “and an amount of antioxidant *effective to stabilize Compound A* from degradation” (emphasis added)). The Court cautioned in its claim construction opinion that it would be “improper to impute the antioxidant’s stabilizing effect on Compound A, explicitly claimed in some claims [*i.e.*, the function claims], into claims that do not contain that explicit limitation [*i.e.*, the presence claims].” (D.I. 250, p. 2). Despite this clear statement, Watson maintains that “antioxidant,” as used in the patents in suit, “requires the presence of an agent that reduces oxidative degradation of some component in the claimed composition.” (D.I. 318, pp. 12-13 (“The definition of ‘antioxidant’ adopted by the Court, ‘an agent that reduces oxidative degradation,’ plainly recognizes that the term is a functional limitation that requires a reduction of oxidative degradation in the claimed composition.”)). This argument is rejected as being inconsistent with the Court’s claim construction.

b. Watson's ANDA products meet every limitation of the presence claims

The parties agree that Watson's ANDA product contains Compound A (PTX 311, p. 1603) and a diluent/carrier. (JTX 56, p. 1823). Only the second limitation requiring "0.01 to 0.5 weight percent" of an antioxidant is in dispute.<sup>5</sup>

Butylhydroxytoluene, or BHT, is well known in the art as an antioxidant. (DTX 11, p. 47; PTX 17, p. 203; JTX 184, p. 1261; JTX 19, p. 441; DTX 55, p. 263). The patents in suit also identify BHT as an antioxidant in the specification and claim BHT as an antioxidant in the asserted claims. '031 patent, 4:11-14 ("The applicant has found that an effective stabilising effect is surprisingly achieved when the antioxidant is selected from . . . butylhydroxytoluene."); *id.*, claim 3 ("A pharmaceutical composition according to claim 1 wherein the antioxidant is . . . butylhydroxytoluene."). Novartis's infringement expert, Dr. Davies, performed tests<sup>6</sup> on Watson's ANDA products that identified the presence of BHT. (Tr. 312:15-21). Watson's expert, Dr. Sessler, admitted that Watson's ANDA products contain BHT (Tr. 398:21-399:1), and Watson itself conceded that BHT may have been introduced into its product by an upstream supplier. (D.I. 318, p. 6 n.2 ("It appears that BHT may have been added to the tackifier component by one of Henkel's suppliers upstream in the polymer manufacturing process and that small amounts of BHT were carried over into Watson's ANDA product as an unreactive impurity.")). This evidence proves that BHT, a well-known antioxidant, is present in Watson's ANDA products.

BHT is present in Watson's ANDA products within the claimed ranges: 0.01 to 0.5 percent by weight of the composition. Dr. Davies tested the 905A adhesive in isolation using gas

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<sup>5</sup> Claim 1 of the '031 patent requires "about" 0.01 to "about" 0.5 percent by weight. This difference is immaterial because, as shown below, the measured amount of antioxidant falls within the 0.01 to 0.5 weight percent range.

<sup>6</sup> The tests Dr. Davies utilized were gas chromatography and gas chromatography coupled with mass spectrometry. (Tr. 311:21-312:21).

chromatography and found BHT at a level of 447 parts per million, which is 0.045 percent. (JTX 41, p. 2; JTX 36; Tr. 320:7-20). After the addition of rivastigmine to the 905A adhesive layer, the BHT concentration is decreased to 0.032 percent. (JTX 41, p. 2; Tr. 320:10-321:17). Dr. Davies then performed the same tests on the 905A/900A adhesive bilayer and measured 0.027 percent BHT. (JTX 41, p. 2; JTX 36). Using these result, Dr. Davies calculated<sup>7</sup> the amount of BHT in the drug-containing 905A layer in two scenarios: 1) all of the BHT remains in the 905A layer but the rivastigmine becomes distributed throughout the 905A/900A adhesive bilayer via diffusion;<sup>8</sup> and 2) BHT and rivastigmine both diffuse and become evenly distributed in the 905A/900A adhesive bilayer. (JTX 41, pp. 1-2). The amount of BHT in the 905A layer under those two scenarios is 0.036 and 0.023 percent by weight, respectively. (*Id.*, p. 2; Tr. 113:15-120:6). In response to criticism from Dr. Sessler, Dr. Davies repeated his experiments using high performance liquid chromatography and ultraviolet spectroscopy. (Tr. 329:13-330:8). These additional tests showed “excellent agreement” with the gas chromatography results and confirmed his earlier findings. (*Id.* at 330:4-14; JTX 51).

In addition to Dr. Sessler’s criticism, Watson advances several other arguments in support of its non-infringement position. Watson points out that “BHT is not identified in any of Watson’s product development reports for the formulation used in Watson’s ANDA product, and BHT is not mentioned anywhere in Watson’s ANDA.” (D.I. 318, p. 6). The fact that those reports did not detect and quantify BHT does not mean no BHT is present. Novartis has shown,

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<sup>7</sup> Dr. Davies was not able to measure the diffusion of BHT experimentally because the BHT level is below the instrument’s limit of detection. (Tr. 328:10-16). Nonetheless, there are several reasons to believe that BHT will diffuse. First, there is no barrier to diffusion between the 905A and 900A adhesive layers. Second, Dr. Davies experimentally confirmed that rivastigmine diffuses through the bilayer. Third, BHT is a smaller molecule than rivastigmine which, generally speaking, means it will more readily diffuse. (Tr. 121:17-122:22).

<sup>8</sup> The adhesive bilayer is a highly diffusible system, allowing the rivastigmine to travel from the 905A layer through the 900A layer and into the patient’s skin. (Tr. 323:15-324:7). Dr. Davies confirmed the diffusion of rivastigmine experimentally through Raman spectroscopy. (Tr. 323:15-329:3; JTX 38).

and Watson now appears to admit (*id.*, p. 6 n.2), that Watson's ANDA products contain BHT. How the BHT entered Watson's product and why previous reports did not quantify the amount of BHT is irrelevant for purposes of infringement. Watson also asserts that Novartis should have conducted additional testing for "BHT daughter products" to prove that the BHT in Watson's ANDA product actually functioned as an antioxidant. (*Id.*, pp. 29-30). This line of testing is not necessary because, as discussed above, the presence claims do not add a functional limitation vis-à-vis the antioxidant.

In summary, the amount of BHT, a known antioxidant, present in both scenarios evaluated by Dr. Davies falls within the amount required in the asserted claims. Watson does not dispute that its ANDA product meets the other claim limitations. (D.I. 310, p. 30). Therefore, Novartis has proven by a preponderance of the evidence that Watson's ANDA product infringes the presence claims of the patents in suit.

## 2. The Function Claims

As explained by the Federal Circuit, patentees are permitted to prove infringement by "any method of analysis that is probative of the fact of infringement, and circumstantial evidence may be sufficient." *Martek Biosciences Corp.*, 579 F.3d at 1372-73 (internal citation omitted) (finding combination of testing and scientific literature sufficient to prove infringement).

According to Watson, Novartis must establish the following three elements to prove infringement of the function claims: "(1) rivastigmine oxidatively degrades in Watson's product; (2) BHT is significantly reducing the oxidative degradation of rivastigmine in Watson's product; and (3) the significant reduction of the oxidative degradation of rivastigmine occurs over a prolonged period of time." (D.I. 318, p. 13). Here, Novartis has proven that free radical generators create an oxidative environment, that Watson's ANDA products contain three known

free radical generators, and that rivastigmine is susceptible to oxidative degradation in the presence of those free radical generators. Despite this oxidative environment, the rivastigmine in Watson's ANDA products undergoes only minimal oxidative degradation over a prolonged period of time. The most logical conclusion is that the BHT in Watson's ANDA products acts as an antioxidant by scavenging free radicals, thereby protecting rivastigmine from oxidative degradation.

a. Watson's ANDA product is an oxidizing environment

Watson's ANDA product is manufactured and stored in an oxidative environment. Oxidative degradation is a type of chemical reaction, caused by the presence of free radicals, "where the substance that is oxidized loses an electron to another substance that is called an oxidant." (Tr. 134:22-135:9). Free radicals are a highly reactive species due to their free or unpaired electrons. (*Id.* at 135:15-19). Species with paired electrons are more stable, so free radicals take electrons from other molecules to pair their free electrons. (*Id.* at 135:20-24). Oxygen, peroxides, and other free radical generators, which include residual monomers, are three common sources of free radicals. (*Id.* at 136:14-137:12). Importantly, chain reactions do not require large quantities of free radicals. (*See, e.g.*, JTX 188, p. 1507 ("Only a very small amount of oxygen is required to initiate a chain reaction."); Tr. 136:22-137:4). Watson's ANDA product is exposed to all three categories of free radical generators, which creates an oxidative environment. The presence of each free radical generator will be discussed in turn.

Every step of Watson's manufacturing process is carried out in the presence of air, which contains oxygen. Rivastigmine is mixed with the 905A adhesive in ambient air, the 905A casting solution is passed through a filter in ambient air, the 905A casting solution is coated onto the release liner in ambient air, the 905A-coated release liner is dried in the presence of "filtered

and heated air,” the backing layer is laminated onto the 905A adhesive in ambient air, the 900A casting solution is coated onto the release liner in ambient air, the 900A-coated release liner is dried in the presence of “filtered and heated air,” and the 900A and 905A adhesive layers are laminated together in ambient air. (JTX 56, pp. 1832-37). The individual product patches are also cut and pouched in ambient air. (*Id.*). Indeed, Dr. Sessler acknowledged during cross-examination that the external environment for each step of the manufacturing process occurs in ambient air. (Tr. 513:4-518:19). It should come as no surprise, therefore, that Dr. Davies found the presence of oxygen inside the pouch containing Watson’s ANDA product in a concentration comparable to that of ambient air. (JTX 54, p. 2; Tr. 339:22-330:14).

Watson raises two counterarguments questioning whether the manufacturing process’s environment is indicative of the oxygen levels in the ANDA product itself. First, Dr. Sessler emphasized that pressurized nitrogen is used to extrude the 905A and 900A adhesive solutions onto the release liners, thereby forming a “nitrogen-saturated solution.” (Tr. 514:10-515:21). Although the nitrogen gas does not stay in the adhesive layer, Dr. Sessler testified that he believed “a blanket of vapor and nitrogen” would form around the adhesive and protect it from oxygen molecules. (*Id.* at 453:2-23). Dr. Sessler did not provide any support for this argument other than the general scientific principle that gas solubility decreases at higher temperature, which would lead to the “out gassing” of nitrogen from the adhesive. (*Id.*). Even if Dr. Sessler was correct in his hypothesis about the nitrogen blanket, the nitrogen blanket would only protect the adhesive from oxygen for the steps following extrusion. There would be no nitrogen blanket for any of the previous steps, each of which was conducted in the environment of ambient air.

Second, Watson criticized Dr. Davies for failing to determine whether oxygen is present in the adhesive bilayer itself. (D.I. 318, p. 15). Dr. Davies was unable to perform direct testing

on the adhesive bilayer both because the bilayer was too thin (on the order of 90 microns thick) and because placing the needle into the bilayer would block the sensor. (Tr. 351:11-22).

Novartis did, however, link the oxygen concentration in the pouch to the oxygen concentration in the adhesive bilayer. The backing layer used in Watson's ANDA product is described by the manufacturer as having "high oxygen transmission rates." (JTX 24, p. 2652; Tr. 165:7-15). Dr. Klibanov, another Novartis expert, testified that the oxygen present in the pouch will "readily penetra[te]" the backing film and enter Watson's ANDA product. (Tr. 165:7-166:15). Indeed, Dr. Sessler agreed that these transdermal patches are *designed* for air to permeate the patch to enhance skin health, which requires that the backing layer allow for the diffusion of oxygen. (*Id.* at 522:13-22). Therefore, it is a logical conclusion that the gases in the pouch, which include oxygen, will enter into Watson's ANDA product.

Watson's ANDA products also contain peroxides. The peroxide value, or peroxide number, test is a well-known method for detecting peroxides. U.S. Patent No. 6,699,498, 2:58-62 ("the '498 patent") ("The peroxide content is commonly expressed by means of the so-called peroxide number."). As described in the U.S. Pharmacopeia, the test "expresses, in milliequivalents of active oxygen, the quantity of peroxide contained in 1000 g of the substance." (JTX 47, p. 152). Using this standard experiment, Dr. Davies tested samples of both the 900A and 905A bulk adhesives and found the presence of peroxides. (JTX 53, p. 2 (noting peroxide values of 1.64 and 1.89 for the 900A adhesive and 0.72 and 1.07 for the 905A adhesive); Tr. 353:17-354:20). In addition to Dr. Davies's testing, Novartis relies on two documents from Henkel, Watson's adhesive manufacturer, showing that peroxides are used in the manufacture of the adhesive and might remain after manufacturing is complete. Henkel lists t-amylperoxypivalate ("TAPP"), a known peroxide, as an ingredient in the 900A adhesive whose

purpose is to scavenge residual monomers. (JTX 23, p. 1; Tr. 174:13-175:5). Moreover, a Henkel employee informed Watson in an email that the 900A adhesive “contains trace amount[s] of residual initiator, which is a peroxide” when Watson inquired about the 900A components. (JTX 32, p. 285088).

Watson offers three arguments in rebuttal. First, Watson contends that the peroxide test used by Dr. Davies does not measure for peroxides. (D.I. 318, p. 17). Watson is technically correct because the peroxide test actually measures the extent to which iodide ions can be oxidized to iodine. However, as Dr. Klivanov explained, the test is conducted under conditions where the measured oxidation is attributable to the presence of peroxides. (Tr. 286:3-287:4 (“Q. So it’s a bit of a misnomer to say [the peroxide value test] measures peroxide. It is not directed to peroxides; correct? A. No. I disagree with that. Q. All right. Well, you wouldn’t disagree that what it actually measures is the extent to which iodide is oxidized to iodine? A. Yes, but it’s done under the conditions where what you measure is a peroxide. That’s the test that is described by the United States Pharmacopeia specifically to determine peroxide oxidation number.”)). Watson believes this is problematic because there are numerous substances other than peroxides that can oxidize iodide to iodine but that are incapable of oxidizing rivastigmine. (D.I. 318, p. 17; Tr. 429:22-430:16). Despite flagging this as a potential issue, neither Dr. Sessler in his trial testimony, nor Watson in its post-trial briefing, offered any scientific literature in support of its position that this test was applied improperly. Watson’s unsubstantiated argument is not persuasive in light of the U.S. Pharmacopeia and a U.S. patent on transdermal devices that both list the peroxide value test as a standard method for determining the quantity of peroxides. (JTX 47, p. 152; ’498 patent, 2:58-62; *see also* Tr. 354:7-11).



Second, Watson asserts the tests Dr. Davies conducted on the samples of bulk 900A and 905A adhesive have no bearing on the peroxide level in Watson's ANDA product. (D.I. 318, p. 17). This, too, is unpersuasive because Dr. Davies explained that testing the adhesives themselves prior to their inclusion in the transdermal device is the standard approach. (Tr. 354:21-355:15). Dr. Sessler agreed on cross examination that the method used by Dr. Davies is taught in the '498 patent, which addresses transdermal systems. (Tr. 526:16-527:9; '498 patent, 3:24-42). In addition, Dr. Davies testified that it would not be practical for him to test the actual ANDA product because he would have to remove the adhesive bilayer from the product. (Tr. 355:16-356:13). This process is difficult and would require roughly 150 patches to obtain enough material to conduct a single test. (*Id.*). Moreover, Dr. Klibanov noted that Watson did not take any steps to remove the peroxides from either the 900A or 905A adhesive layer, so it stands to reason that the peroxides will still be present when those two peroxide-containing layers are combined to form a bilayer. (*Id.* at 179:7-18).

Finally, Watson disagrees over the import of the Henkel documents cited by Novartis. The fact that Henkel uses TAPP in the manufacturing process proves nothing, according to Watson, because TAPP is used as a monomer scavenger. (D.I. 318, p. 20). Monomer scavengers are consumed during the manufacturing process so Watson posits there is no reason to believe that TAPP carries over to the ANDA product,<sup>9</sup> and Novartis did not conduct any tests to confirm its theory. (Tr. 439:13-24). It is true that Novartis did not perform experiments to determine if residual TAPP is present in Watson's ANDA product. The identity of the particular peroxide(s) present in Watson's ANDA product, however, is immaterial. Novartis has shown through Dr. Davies's experiments that a measureable amount of peroxide is present, and this is

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<sup>9</sup> Although not dispositive, the certificate of analysis for the 900A adhesive does not list TAPP as a component. (JTX 186, p. 2644; Tr. 255:13-256:10).

sufficient to conclude that Watson's ANDA product is at least a minimally oxidative environment.<sup>10</sup> Watson also criticizes the Henkel email as informal hearsay from someone who was never deposed and who did not testify at trial. (D.I. 318, p. 20). In concluding that Watson's ANDA product contains peroxides, the Court does not rely on the Henkel email alone. The email is simply one piece of evidence, corroborated by Dr. Davies's experimental findings, indicating peroxides are present. It should also be noted Watson offered no objection to the exhibit at trial. (Tr. 173:11-174:2).

Residual monomers, a type of free radical generator, are present in Watson's ANDA product. Henkel's specification document for the 900A adhesive states that "residual levels of the starting monomers may be present in the final product" because polymerization "is never 100% efficient." (JTX 23, p. 1). There is a section of the specification titled "Residual Monomers" that lists the maximum specified limits for each monomer that can be present. (*Id.*). Some of these limits for the individual monomers are as high as 700 ppm, and if all listed monomers were present in their maximum specified amounts it would exceed 1500 ppm. (*Id.*). Another Henkel document, the certificate of analysis, lists what is actually present in the product, as opposed to the specification which denotes what is permitted in the product. (Tr. 182:3-13). The certificate of analysis for the 900A adhesive identified the presence of four residual monomers at a combined concentration of 606 ppm. (JTX 186, p. 2644; Tr. 182:3-184:12; *see also* JTX 30, p. 279745 (reporting 388 ppm of residual monomers in a different batch of 900A adhesive)).

Watson does not substantively dispute that residual monomers are present in its ANDA products. Instead, Watson contends the amount of residual monomers is insufficient to cause

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<sup>10</sup> Watson's arguments regarding whether the peroxides have the "power" to oxidatively degrade rivastigmine are addressed below.

rivastigmine degradation, and argues that the presence of residual monomers does not create an oxidative environment. The first point is addressed in a subsequent section. As for the second point, Dr. Sessler explained that residual monomers, by themselves, cannot lead to oxidative degradation. (Tr. 457:3-8). He did admit, however, that residual monomers are an “easy-to-detect” surrogate for the corresponding monomer radical. (*Id.* at 526:9-15). In order for residual monomers to form monomer radicals and cause oxidative degradation, “[t]hey would have to react[, f]or instance, with peroxides, with activated forms of oxygen.” (*Id.* at 458:10-23). As discussed above, peroxides are present in Watson’s ANDA product. The presence of residual monomers working in tandem with other impurities such as peroxides creates an oxidative environment.

Novartis also alleges that polymerization initiators are present in Watson’s ANDA product. Polymerization initiators are used in the manufacture of polymers, such as the 900A adhesive, and are capable of creating an oxidative environment. (JTX 23, p. 1; Tr. 421:7-19). According to Novartis, the “3M Patent Application shows that, in the absence of washing, residual initiator carries through to the final patches.” (D.I. 322, p. 10; *see also* JTX 17, p. 7 (“Such polymerization reactions result in the formation of a polymer along with some level of unreacted monomers and initiator.”)). This argument is not persuasive.<sup>11</sup> Unlike the residual monomers, the 900A specification does not say anything about residual polymerization initiator (JTX 23, p. 1), and polymerization initiator is not listed as being present in the certificate of analysis for the 900A adhesive. (JTX 186, p. 2644; JTX 30, p. 279745). Additionally, Novartis

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<sup>11</sup> Novartis also cites an email from a Henkel employee stating that the 900A adhesive contains residual peroxide initiator as proof that TAPP is a component in Watson’s ANDA product. (JTX 32, p. 285088; D.I. 322, p. 8). The Court relied on this email when Novartis cited it to show the presence of peroxides because there was other scientific evidence to corroborate that position. Here, aside from expert testimony and analogies based on other adhesive systems, the email is the only offered proof Novartis has that Watson’s ANDA product contains residual initiator. It is also worth noting that TAPP is listed in the 900A specification as a monomer scavenger, not an initiator. (JTX 23, p. 1).

did not conduct any testing on the adhesives for Watson's ANDA product to establish the initiator's presence. It is possible an incomplete polymerization reaction in the 900A polymer left behind unreacted initiator, as Dr. Klibanov maintained (Tr. 179:19-181:20), but more concrete evidence is required to support that proposition. Reliance by analogy on a different patent application with a different adhesive is insufficient to prove that initiator in the 900A polymer adhesive carries over to the finished Watson ANDA product.

In sum, an oxidizing environment can be created by the presence of oxygen, peroxides, or other free radical generators. In this case, all three types of free radical generators can be found in Watson's ANDA products. Ambient air is not excluded from the manufacturing environment for Watson's ANDA products and was found to be present inside Watson's pouches. Dr. Davies tested the 900A and 905A adhesives and found peroxides, which Dr. Klibanov explained would be carried forward into Watson's ANDA product because no steps were taken to remove these impurities. Similarly, the documentation provided by Henkel shows that residual monomers are present in the 900A adhesive and are not removed prior to the assembly of Watson's ANDA product. The presence of these three free radical generators constitutes sufficient proof that Watson's ANDA product is an oxidizing environment.

b. Rivastigmine is susceptible to oxidative degradation in an oxidative environment

There is no dispute that rivastigmine is susceptible to degradation depending on the particular environment to which it is exposed. (Tr. 522:23-523:3). As discussed above, the environment for Watson's ANDA product contains oxygen, peroxides, and residual monomers. The question becomes whether these substances can oxidatively degrade rivastigmine. The answer to that question is yes, based on the evidence Novartis put forth regarding the individual

and collective effects of oxygen, peroxides, and residual monomers on rivastigmine. Each free radical generator's effect on rivastigmine will be discussed in turn.

Rivastigmine oxidatively degrades in the presence of oxygen. The patents in suit teach that rivastigmine in a transdermal device will degrade if exposed to oxygen despite "the formation of an occlusive polymer matrix around compound A [rivastigmine] and its storage in air-tight packaging." '031 patent, 1:22-28 ("It has now been found after exhaustive testing that compound A is susceptible to degradation, particularly in the presence of oxygen."). Novartis's experiments also showed that oxygen caused degradation to rivastigmine in its bulk form. (JTX 85, p. 2403 ("Rivastigmine base as liquid is very sensitive to oxygen (air) and moisture. Degradation is accelerated by the influence of heat.")). Indeed, Watson's own documents acknowledge oxygen's effects on rivastigmine. (JTX 29, p. 29808 ("Rivastigmine is subject to both hydrolytic and oxidative degradation.")).

Watson relies on a two-prong argument articulated by Dr. Sessler: "[F]or oxidative degradation to occur, oxygen must have both the 'power' to oxidize rivastigmine and must be present in a sufficient 'amount.'" (D.I. 318, p. 15). With respect to the first point, Dr. Sessler explained that molecular oxygen alone is insufficient to oxidatively degrade rivastigmine; instead, oxygen must react with another substance, such as a metal ion, to form a reactive oxygen species. (Tr. 443:1-23; *id.* at 420:1-24). Watson alleges that Novartis's failure to test for these other substances results in a failure to prove oxidative power. (D.I. 318, p. 15). Second, the amount of oxygen is important because of its role in the oxidation. Oxygen is not just an initiator; it is consumed in the reaction and incorporated into the ketone degradation product. Watson claims to use pressurized nitrogen gas to extrude the adhesives and a roller to squeeze all

of the air from its pouches prior to sealing,<sup>12</sup> both of which protect its ANDA product from oxygen. (*Id.*, p. 16). Therefore, the argument goes, “[w]ithout knowing the amount of oxygen, if any, in the adhesive system of the patch itself, it is impossible to determine whether enough oxygen is present to form the rivastigmine degradants.” (*Id.*).

Dr. Sessler’s concerns about oxygen’s power to oxidize rivastigmine are overstated. Regardless of whether oxygen is labeled as a “strong” or “weak” oxidant in the organic environment, the need to protect the active substance in a transdermal patch from oxygen is well documented in the literature. (’031 patent, 1:22-28; ’498 patent, 1:44-47 (“[T]he stability of the active substance and of the auxiliaries may be put at risk by reaction with active oxygen. Such active oxygen is, naturally, the oxygen of the air.”); JTX 9, p. 110 (recognizing that oxidation may “occur spontaneously under the initial influence of atmospheric oxygen”); JTX 188, p. 1507). Even if oxygen is a relatively weak oxidant, as Dr. Sessler testified (Tr. 443:7-23 (“I’ve seen no evidence that under the normal conditions of Watson’s ANDA product, manufacture, storage, transport, [and] use, that oxygen is even capable of triggering oxidative degradation. . . . Oxygen-based oxidation becomes weaker in an organic environment.”)), he also conceded that peroxides and residual monomer radicals, in addition to metal ions, can create activated oxygen that would have the power to degrade rivastigmine. (*Id.* at 419:13-420:24 (“I think for oxygen to do its oxidative degradation, it has to be converted to some sort of active form. . . . Residual radicals left over perhaps from the polymerization process can trigger that kind of activation. Peroxides, as we’ve discussed, can either induce that kind of activation or act as an oxidant on their own.”)). The presence of both peroxides and residual monomers leaves little doubt that

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<sup>12</sup> The Court agrees with Novartis that it could not find any reference to a roller that squeezes air from the pouches in the cited portions of Watson’s ANDA. (D.I. 318, p. 16; D.I. 322, p. 5; JTX 56, pp. 1830, 1834).

oxygen has the power required to oxidize rivastigmine in the environment of Watson's ANDA product.

Watson's second argument also misses the mark because the steps Watson took to eliminate air from its ANDA product were verifiably ineffective. There was a large enough volume of gas inside Watson's pouch to form a visible bubble when Dr. Davies rolled up the patch. (*Id.* at 340:15-341:21). Dr. Davies tested this gas with an oxygen meter and found the presence of oxygen in a concentration similar to that of ambient air. (JTX 54, p. 2; Tr. 340:8-14). It is highly probable the oxygen in the pouch will enter Watson's ANDA product because the patch was designed to be breathable. (Tr. 522:13-22). This is affirmed by Watson's acceleration lifetime studies, which prove that the amount of oxygen in the pouch is sufficient to oxidize rivastigmine because the ketone degradant is detected after 12 weeks of storage under normal conditions.<sup>13</sup> (JTX 195, p. 78375 (noting presence of ketone degradant at every time point from 12 weeks to 78 weeks under normal storage conditions)). When "stressed" conditions were applied, the ketone degradant appeared after just 4 weeks. (*Id.*).

Peroxides are also capable of oxidatively degrading rivastigmine, but most likely not at the levels measured by Dr. Davies. In order to reduce oxidative degradation, the '498 patent teaches that "an upper peroxide number limit of 20, better still 10, preferably 5, should not be exceeded." '498 patent, 7:16-17. Dr. Davies measured peroxide values of less than 2 in Watson's ANDA product (JTX 53, p. 2), which is well within what Watson describes as the "safe zone" taught by the '498 patent. (D.I. 318, p. 19). Novartis responds by pointing to a

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<sup>13</sup> Given that the amount of ketone degradant detected in Watson's stability studies is unchanged over time within the limits of measurement precision, Watson suggests it could be due to the introduction of a trace impurity prior to the formation of the ANDA product. (D.I. 318, p. 23 n.14). This argument is unavailing in light of the weight of direct and circumstantial evidence proffered by Novartis.

different section of the '498 patent's specification that states "[a]n additional improvement in stability may be achieved by the addition of antioxidants," even if "the materials are virtually free from peroxides." '498 patent, 7:8-12. Given the diverging opinions from two highly qualified experts (*Compare* Tr. 189:23-190:13, *with* Tr. 429:22-430:21), this issue turns on their respective credibility as evaluated during the trial. The Court finds the teachings of the '498 patent and Dr. Sessler's trial testimony to be more persuasive. The low level of peroxides is unlikely to oxidatively degrade rivastigmine.

The fact that the peroxides, by themselves, likely are not present in sufficient quantities to cause oxidative degradation does not end the inquiry. As Dr. Klibanov noted, all three of the free radical generators discussed can create an oxidative environment that will lead to the oxidative degradation of rivastigmine. (Tr. 189:23-190:13). Peroxides can also react with oxygen and residual monomers to form activated oxygen and monomer radicals, both of which can also degrade rivastigmine. The low level of peroxides, therefore, does not alter the Court's view that rivastigmine is susceptible to degradation in Watson's ANDA product.

Finally, residual monomers, when present with other impurities known to exist in Watson's ANDA product, have the power to oxidize rivastigmine. Dr. Sessler stated this himself. (Tr. 458:10-23). As shown above, residual monomers are present in the 900A adhesive and also in Watson's ANDA product. Watson responds by arguing that the concentration of residual monomers is not sufficient to cause oxidative degradation. (D.I. 318, pp. 21-22). The 3M patent application, relied on by both parties, states, "The polymerization reaction product is washed such that the at least two ethylenically unsaturated monomers, if present in the adhesive as unreacted monomers after washing, are reduce[d] to a level of less than 200 ppm of total unreacted monomer, based upon the total weight of the adhesive." (JTX 17, p. 6). The 900A



adhesive, which contained 388 and 606 ppm residual monomers in the two certificates of analysis (JTX 186, p. 2644; JTX 30, p. 279745), represents only 34.7% of the total weight of the adhesive. (JTX 56, p. 1823). When the residual monomer concentration is adjusted based on the weight of the total adhesive, as taught in the 3M patent application, the resulting concentrations in the adhesive bilayer are 134 and 210 ppm, respectively.<sup>14</sup> (D.I. 318, p. 22). Watson contends that there is no oxidative environment because one value is substantially below the 200 ppm goal for washed adhesives taught by the 3M patent application, and the other value is only marginally above it. (*Id.*).

It is true that the 3M patent application suggests it is desirable to achieve less than 200 ppm of residual monomer by washing the polymerization reaction product. (JTX 17, p. 6). Although it recognizes that some embodiments may be stable after the washing process without the need to add an antioxidant, other embodiments will simply require a lesser amount of antioxidant to attain stability. (*Id.*). The need for an antioxidant is demonstrated by 3M's own experiments showing 0.95% oxidative degradation of rivastigmine occurred after two months at 60°C in a copolymer with no antioxidant, despite having a residual monomer concentration below the detection limit. (*Id.*, pp. 20-22; D.I. 322, pp. 9-10). Although the parties disagree on whether the level of residual monomers in Watson's ANDA product is sufficient to oxidatively degrade rivastigmine, the Court finds Novartis's position to be more credible.

It is clear that rivastigmine is subject to oxidative degradation in the presence of oxygen, peroxides, and residual monomers. It is also clear that each of these three free radical sources

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<sup>14</sup> The concentrations of residual monomer in the adhesive bilayer were obtained by multiplying 34.7% by the residual monomer concentration in the 900A adhesive. This appears to assume that there are no residual monomers in the 905A adhesive, and, for purposes of this argument, the Court follows that assumption.

are present in Watson's ANDA products. This leads to the conclusion that Watson's ANDA products contain an environment in which one would expect rivastigmine to oxidatively degrade.

c. Rivastigmine does not significantly degrade in Watson's ANDA product and the most likely explanation is that BHT acts as an antioxidant

Watson's ANDA states that its products exhibit only a "low level of impurities and degradation products" when subjected to stress tests designed to predict degradation over a prolonged period of time. (JTX 56, p. 1826; Tr. 698:24-699:9). Based on its choices of excipients, Watson expected its ANDA product to maintain stability throughout the intended shelf life. (*Id.*). Watson's ANDA product also contains BHT. Dr. Kibbe, Watson's obviousness expert, admitted that the concentration of BHT claimed in the patents, and present in Watson's ANDA products, falls within what is "typically used in most pharmaceutical formulations." (Tr. 629:11-24; *see also* DTX 11, p. 47 (listing typical BHT concentrations for various uses)). This belies Watson's contention that "Plaintiffs have not presented any evidence that the small amounts of BHT at the levels detected by Dr. Davies could reduce oxidative degradation of rivastigmine in any formulation, much less in the environment of Watson's ANDA product." (D.I. 318, pp. 6-7). Dr. Klivanov offered the following explanation for the low level of degradation:

Well, I think that one of skill in the art looking at this question will say [] we have rivastigmine, which is undeniably susceptible to oxidative degradation. You also have all this oxidative environment within Watson's adhesive bilayer. We have oxygen. We have peroxide[s]. We have residual initiators and monomers. And it's been shown that each one of those can lead to oxidative degradation [] of rivastigmine. And nevertheless, there is no significant oxidation of rivastigmine for a prolonged period of time. So one of skill in the art would look at that data and say, What is the most likely explanation for that? And [the] most likely explanation for that is that the BHT, which is undeniably present in the products affords significant stabilization for rivastigmine.

(Tr. 197:10-198:5).<sup>15</sup>

Watson criticizes Dr. Klibanov's analysis for incorrectly assuming that using an antioxidant and excluding oxygen are the only ways to prevent oxidative degradation in a transdermal product. (D.I. 318, p. 24). For example, Watson points to the '498 patent as evidence that the risk of oxidative degradation can be avoided by keeping the peroxide value number below 20—the peroxide value numbers measured by Dr. Davies in the 900A and 905A adhesives were less than 2. (*Id.*; '498 patent, 7:14-17). The '498 patent, however, addresses only oxidative degradation caused by peroxides. Residual monomers are not discussed, and excluding oxygen is suggested by the '498 patent. '498 patent, 1:44-50. Watson's argument would be more compelling if its ANDA product contained only peroxides. The facts of this case, however, are quite different, and Watson's ANDA product has been proven to contain both oxygen and residual monomers in addition to peroxides. Therefore, the teachings of the '498 patent are not directly on point and cannot support the broad assertion advanced by Watson that, independent of other impurities, a peroxide value number of less than 20 means oxidative degradation will be avoided.

Watson relies on the patents in suit for the proposition that trace amounts of free radicals will not negatively affect rivastigmine's stability. '031 patent, 1:44-46 ("The diluent or carrier may contain trace amounts of free radicals without affecting the stability of the pharmaceutical

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<sup>15</sup> Novartis attempts to bolster Dr. Klibanov's opinion with Watson's experimental data on a prototype adhesive, the 9301 adhesive. (D.I. 310, p. 20). Watson conducted a stability test on the 9301 adhesive and found the degradation of rivastigmine without BHT to be significantly higher than the degradation of rivastigmine with BHT after 67 weeks. (JTX 205, pp. 25917-18 (finding addition of BHT resulted in between three and five fold decrease in rivastigmine degradation at both 25 and 40 degrees Celsius)). Watson decided not to pursue the 9301 adhesive, and it is not used in Watson's ANDA product. (Tr. 203:3-9). The 9301 adhesive is a very different formulation than the 900A and 905A adhesives: it uses a different polymerization initiator at a different concentration (*Compare* JTX 32, p. 285091, *with* JTX 23, p. 1), and contains vastly different concentrations of BHT. (*Compare* JTX 205 p. 25917, *with* JTX 41, p. 2). These experiments are certainly relevant in the sense that they demonstrate BHT's effect on rivastigmine degradation in the 9301 adhesive. The relevance to Watson's ANDA product and this case, however, is minimal given the number of differences between the adhesives and their constituent components.

composition.”). It follows, according to Watson, that “the presence of some amount of free radicals in a transdermal system does not necessarily lead to an oxidative degradation problem.” (D.I. 318, p. 24). The Court disagrees. The patents in suit contain an antioxidant, which assists in preventing oxidative degradation. It is more reasonable to conclude that the antioxidant shields rivastigmine from the free radicals’ harmful effects than to conclude that free radicals do not create an oxidative environment. *See* ’031 patent, 1:34-36.

Watson also asserts that Novartis should have performed additional testing. (D.I. 318, pp. 27-30). This argument is unavailing. The testing and other experimental data Novartis presented are sufficient to prove infringement by a preponderance of the evidence.

Watson’s final argument is that Dr. Sessler’s “footprint” hypothesis disproves Novartis’s theory that BHT is acting as an antioxidant in Watson’s ANDA product. Dr. Sessler posits that an antioxidant leaves a characteristic “footprint” involving the ratio of the degradants. According to the theory, rivastigmine degradation results in two main degradants, a styrene degradant and a ketone degradant, in approximately a 1:1 ratio. The styrene degradant forms first, and it can subsequently be oxidized to form the ketone degradant if an oxygen atom source is present. Unlike the styrene degradant, which can be formed via a non-oxidative pathway, the ketone degradant can only be formed through oxidation and consumes an oxygen atom in the process. The presence of an antioxidant will disrupt the oxidation reaction, blocking the ketone degradant’s formation in the process. Therefore, the theory predicts the presence of a functioning antioxidant will result in more styrene degradant relative to the ketone degradant. (D.I. 318, p. 25 (citing various portions of Dr. Sessler’s trial testimony)).

No experimentation was done to validate the theory,<sup>16</sup> but at trial both parties tested the theory's predictions by applying it to existing data. Watson supported its theory with a Novartis stability study on its transdermal device that found more ketone degradant than styrene degradant when no antioxidant was present, but more styrene degradant than ketone degradant when various antioxidants were added. (JTX 187, p. 504460). Novartis pointed to its stress tests on bulk rivastigmine, with no antioxidant present, which did not display the expected 1:1 ratio. The temperature and relative humidity were varied in the four experiments, and only one of the four demonstrated a 1:1 ratio. (JTX 85, p. 2399). In another Novartis test applying forced conditions to bulk rivastigmine, researchers observed a ketone to styrene ratio of nearly two-to-one. (*Id.*, p. 2401). Dr. Sessler attempted to fit this inconsistency into his theory by hypothesizing that oxygen is not a limiting reactant for bulk rivastigmine, but is limiting in a polymeric formulation. (Tr. 491:10-492:14 (citing JTX 195, p. 78375)). If that were the case, more of the ketone degradant would form with bulk rivastigmine because of the excess oxygen. (*Id.*). Although further experimentation may verify Dr. Sessler's theory in due course, the scientific evidence supporting the theory at this juncture is not robust enough for the Court to place its full faith in it.

Even if the "footprint" theory holds, however, its application to Watson's long-term stability test appears to be consistent with the presence of an antioxidant. The presence of an antioxidant, according to the theory, will result in a greater amount of styrene degradant than ketone degradant. In long-term stability testing done on Watson's ANDA product, the styrene and ketone degradant appeared in a 3:2 ratio. (JTX 195, p. 78375 (measuring approximately 0.03% styrene to 0.02% ketone by weight at time points between 26 and 78 weeks)). This is

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<sup>16</sup> The exact rivastigmine degradation pathway underpinning the theory has not been scientifically established. (Tr. 556:13-23). Dr. Sessler himself described it as a "wonderful research study" that he did not conduct. (*Id.*).

entirely consistent with Novartis's contention that Watson's ANDA product contains an acting antioxidant, namely BHT. Dr. Sessler viewed this study's results differently, contending that the reported weight percentages were at the limits of precision. (Tr. 490:5-24). Because the numbers were so small, Dr. Sessler concluded the ratio at each time point was essentially 1:1 and that no antioxidant was present in the system. (*Id.* at 490:5-491:4). Without knowing the margin of error in the measurements it is impossible to tell with statistical certainty whether a ratio of 0.03:0.02 is really a 1:1 ratio. But three data points taken after 78 weeks were measured out to the thousandths decimal place and resulted in ratios of 0.029:0.021, 0.030:0.019, and 0.030:0.021. (JTX 195, p. 78375). All three figures after the decimal point are significant in each of those measurements, making it more likely that it is a 3:2 ratio. At the very least, based on the number of significant figures, the Court is not convinced they represent 1:1 ratios, as Dr. Sessler urges.

In sum, the Court reaches the same logical conclusion as Dr. Klibanov did.

Rivastigmine, which is susceptible to oxidative degradation, and BHT, an antioxidant, are placed in a demonstrably oxidative environment, yet no significant degradation is observed over a prolonged period of time. The most likely explanation, and an explanation that Novartis has proven by a preponderance of the evidence, is that BHT is acting as an antioxidant to protect rivastigmine from oxidative degradation over a prolonged period of time.

## **II. OBVIOUSNESS**

Watson asserts claims 2 and 7 of the '023 patent and claims 3, 7, 13, 16, and 18 of the '031 patent are invalid because the addition of an antioxidant to a rivastigmine transdermal patch would have been obvious to a person having ordinary skill in the art ("PHOSITA") in January 1998—the priority date. (D.I. 311, pp. 2-5; Tr. 34:6-8). This argument is premised on three

major pieces of prior art. The first piece of prior art is a British patent application, GB 2 203 040 A (“GB ’040”), which was filed in 1988. GB ’040 discloses rivastigmine’s use in treating Alzheimer’s disease and suggests a weight percent range of rivastigmine that would be effective in a transdermal device. (JTX 97, pp. 281395-97, 281408-11). The only limitation of the ’023 and ’031 patents’ asserted claims not disclosed by GB ’040 is the addition of an antioxidant. The second prior art reference is U.S. Patent No. 4,948,807 (“the ’807 patent”), which issued in 1990. The purpose of the ’807 patent is to identify alternatives to physostigmine, an acetylcholinesterase inhibitor used in the treatment of Alzheimer’s disease that had several disadvantages, including chemical instability. ’807 patent, 3:37-48. The ’807 patent teaches that sterile injectable formulations of the “compounds of the invention,” including the racemate RA<sub>7</sub>, can incorporate an antioxidant. *Id.*, 7:15-53. The third piece of prior art is a scientific paper written in 1991 by Elmalem *et al.* The Elmalem article compared the effects of three new anti-acetylcholinesterase agents, one of which was RA<sub>7</sub>, with that of physostigmine. (JTX 159, p. 1059). The “Methods” section described the preparation of the drugs in a saline solution with metabisulphite, a known antioxidant. (*Id.*, p. 1060).

Novartis counters that Watson failed to show by clear and convincing evidence that: a PHOSITA would have chosen GB ’040’s rivastigmine transdermal formulation as a starting point, rivastigmine was known in the art to be susceptible to oxidative degradation, and the use of an antioxidant would have been a predictable solution to rivastigmine’s oxidative degradation problem. (D.I. 317, p. 7).

The obviousness inquiry must be conducted from the PHOSITA’s point of view. The parties agree the PHOSITA has an advanced degree in pharmaceuticals, chemistry, pharmaceutical chemistry, materials engineering, or the like, and at least two years of experience developing

pharmaceutical formulations. A PHOSITA could also possess a Bachelor's or Master's degree, provided the PHOSITA has practical experience working in the industry, or academia, for a longer period of time. (Tr. 589:1-590:3; *id.* at 817:13-818:21).

#### **A. Legal Standard**

The presumption that all patents are valid is the starting point for any obviousness determination. 35 U.S.C. § 282 (2012). Under § 103(a), a patent “may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.” *Id.* § 103(a). 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 Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1347 (Fed. Cir. 2012). The improvement over the prior art must be “more than the predictable use of prior art elements according to their established functions.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

To prove obviousness, Watson must show that a 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. Findings of Fact**

1. GB '040, the '807 patent, and the Elmalem article are all prior art.
2. The use of rivastigmine in a transdermal patch to treat Alzheimer's disease was known.
3. Rivastigmine was not known to be susceptible to oxidative degradation.
4. Neither the '807 patent nor the Elmalem article teach a PHOSITA that rivastigmine is susceptible to oxidative degradation.
5. It would not have been obvious to a PHOSITA to combine an antioxidant with rivastigmine in a transdermal patch.

### **C. Conclusions of Law**

Watson contends a PHOSITA would have been motivated to develop a rivastigmine transdermal patch based on the teachings of GB '040, the closest piece of prior art to the patents in suit. GB '040 documents rivastigmine's efficacy in the treatment of Alzheimer's disease, and discloses therapeutic benefits that can be obtained through the use of a transdermal formulation. The '807 patent and the Elmalem article disclose the combination of RA<sub>7</sub><sup>17</sup> with an antioxidant, which teaches a PHOSITA that RA<sub>7</sub> is susceptible to oxidative degradation and recognizes the addition of an antioxidant as a solution to the problem. Therefore, Watson contends, a PHOSITA seeking to improve upon the rivastigmine transdermal device of GB '040, or any other rivastigmine formulation, would have conducted routine stability testing and would have been motivated to add an antioxidant if any oxidative degradation were identified.

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<sup>17</sup> Dr. Klibanov agrees the stability of RA<sub>7</sub> and rivastigmine is identical. (Tr. 896:2-5 (“[T]he Court will remember that stability toward oxidative degradation of rivastigmine[] and RA<sub>7</sub> is the same, and it’s not a controversial issue.”)).

This argument is a logical one, but it overstates the teachings contained in these prior art references. Neither the '807 patent nor the Elmalem article teach a PHOSITA that rivastigmine is susceptible to oxidative degradation. These references certainly disclose that an antioxidant *can* be added to RA<sub>7</sub>, but there is no accompanying suggestion that RA<sub>7</sub> is susceptible to oxidative degradation or that an antioxidant is needed. Without a motivation to add an antioxidant to the rivastigmine transdermal device disclosed in GB '040, Watson's obviousness case falls short.

#### 1. GB '040

As discussed briefly above, GB '040 discloses many limitations of the claims at issue. It discusses both the free base and acid addition salt forms of rivastigmine (JTX 97, pp. 281396-97) and recognizes rivastigmine's ability for "marked and selective inhibition of the acetylcholinesterase" (*id.*, p. 281397), which makes it useful for the treatment of Alzheimer's disease. (*Id.*, p. 281395). GB '040 also acknowledges some advantageous aspects of transdermal delivery<sup>18</sup> with respect to drug tolerability including "long-lasting and constant inhibition of acetylcholinesterase activity" and a "slow onset of action." (*Id.*, p. 281408). Finally, GB '040 discloses a therapeutically effective dose of rivastigmine, for example "about 1 to about 20 % by weight of active agent" (*id.*, p. 281411), which falls within the range of the asserted claims, and it discusses the use of a diluent or carrier. (*Id.*). Both parties' experts agree GB '040 did not disclose or otherwise suggest that rivastigmine, in any formulation, was susceptible to oxidative degradation. (Tr. 710:16-711:5; *id.* at 834:16-24).

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<sup>18</sup> Although GB '040 highlights several benefits of transdermal formulations, that cannot be fairly characterized as the patent application's main purpose. The virtues of other formulation methods were also discussed (JTX 97, p. 281398), and the central innovation of GB '040 is the "surprising[]" and "unexpected" discovery of rivastigmine's selective inhibition of acetylcholinesterase. (*Id.*, p. 281397).

A PHOSITA would not have been motivated to include an antioxidant in any formulation unless there was evidence of oxidative degradation. Excipients, including antioxidants, are inactive ingredients of a pharmaceutical composition that are added to ensure the drug performs its function in a desirable fashion. (*Id.* at 836:22-837:18). The excipients themselves offer no therapeutic benefit. (*Id.* at 837:11-18). In fact, excipients can be incompatible with the drug or other excipients in the pharmaceutical composition, which could lead to a deleterious effect on the drug's performance. (*Id.* at 838:22-840:12 (quoting JTX 188, p. 1507)). The compatibility of an excipient with a given pharmaceutical composition cannot be predicted without experimentation because of the numerous possible chemical reactions. (*Id.* at 841:21-842:3). For this reason, the European Agency for the Evaluation of Medicinal Products—the FDA's European equivalent—instructed, “Antioxidants should only be included in a formulation if it has been proved that their use cannot be avoided.” (JTX 105, p. 2).

Moreover, oxidative degradation is not the only degradation pathway; there were many known types of degradation at the time of the invention. These include hydrolysis, reduction, racemization, photolysis, and pyrolysis. (Tr. 812:10-17; *id.* at 825:21-826:9). But not every drug in every formulation is susceptible to all types of degradation, and, due to the risk of incompatibility discussed above, a PHOSITA would not have added an excipient to prevent each of these types of degradation. A PHOSITA would only be motivated to address and correct known degradation problems. (*Id.* at 811:19-812:9). Because GB '040 was silent with respect to rivastigmine's instability, this motivation would have had to come from some other prior art reference.

## 2. The '807 Patent

Although the '807 patent does disclose the addition of an antioxidant to RA<sub>7</sub>, it does not teach a PHOSITA that RA<sub>7</sub> oxidatively degrades. The purpose of the '807 patent is to identify alternatives to physostigmine, an anti-acetylcholinesterase that lacked the desired chemical stability. '807 patent, 3:37-39. The patent discloses a general formula for a large number of phenyl carbamate compounds—in excess of 8 million (Tr. 847:23-848:16)—several of which were selected for further testing, including RA<sub>7</sub>. '807 patent, 4:21-53; *id.*, tbls. 1-3. RA<sub>7</sub> is one of the compounds identified and later claimed by the '807 patent. The '807 patent discusses the use of RA<sub>7</sub> in tablets, capsules, and elixirs for oral administration, as well as sterile solutions and suspensions for parenteral administration. *Id.*, 7:15-19. Among the “adjuvants” that can be used with tablets and capsules are: binders, excipients, disintegrating agents, lubricants, sweetening agents, and flavoring agents. *Id.*, 7:27-35. The patent provides similar, shorter lists of adjuvants for capsules and elixirs. *Id.*, 7:35-44. For sterile compositions, however, the '807 patents states, “Buffers, preservatives, antioxidants and the like can be incorporated as required.” *Id.*, 7:45-50. The patent then lists several preferred antioxidants.

At first glance, this statement appears to support the proposition for which Watson cited it: namely, that it teaches a PHOSITA that RA<sub>7</sub> is susceptible to oxidative degradation and needs an antioxidant to maintain stability. But despite the laundry list of compounds that “can be incorporated,” there is no specific example in the '807 patent combining RA<sub>7</sub> with an antioxidant. (Tr. 719:16-720:14). Moreover, the '807 patent disclosed the addition of an antioxidant “as required,” yet nothing in the '807 patent suggests RA<sub>7</sub> requires an antioxidant (*id.* at 718:20-719:15; *id.* at 861:5-862:3), and there is no discussion of the appropriate amount of antioxidant, if required, that should be used for any of the compounds. (*Id.* at 862:6-13). There

is no mention of any observed oxidative degradation of RA<sub>7</sub>, and the patent contains no stability data. (*Id.* at 715:24-716:22; *id.* at 863:2-24). To the extent stability is mentioned in the '807 patent, it portrays RA<sub>7</sub> and the other compounds of the invention in a positive light. *See* '807 patent, 11:26-35 (positing that the superior *in vivo* potency of the compounds of the invention may be due to their greater chemical stability relative to physostigmine); *id.*, 3:37-39 (recognizing one of the patent's purposes as "provid[ing] new carbamate derivatives which show greater chemical stability than physostigmine"). Finally, it is worth noting that the patent examiner for the '023 and '031 patents considered both the '807 patent and U.S. Patent No. 5,602,176, which is the American equivalent of GB '040. (JTX 3, pp. 1063, 1083; JTX 4, p. 914; Tr. 830:4-831:14; *see also Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) (explaining that "whether a reference was before the PTO goes to the weight of the evidence," and "it may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered")). When reading this reference as a whole, it would not teach a PHOSITA that an antioxidant was required to protect rivastigmine from oxidative degradation.<sup>19</sup>

### 3. The Elmalem Article

The Elmalem article also fails to teach a PHOSITA of rivastigmine's susceptibility to oxidative degradation. Elmalem compares the effects of three phenyl carbamate compounds with physostigmine on the morphine-induced respiratory depression in rabbits. (JTX 159, p. 1059). One of the phenyl carbamate drugs tested was RA<sub>7</sub>. The key sentence is found in the

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<sup>19</sup> Unlike the other asserted claims, which Waton argues are obvious in light of GB '040 in combination with other prior art references, Watson asserts claim 16 of the '031 patent would be obvious in light of the '807 patent alone and claim 18 of the '031 patent would be obvious in light of the '807 patent and *The Handbook of Pharmaceutical Excipients*. Because the '807 patent does not teach a PHOSITA that rivastigmine is susceptible to oxidative degradation and requires the protection of an antioxidant to maintain stability, its statement that an antioxidant can be incorporated as required does not render the method in claims 16 or 18 of the '031 patent obvious.

“Methods” section of the paper, which states: “All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation.” (*Id.*, p. 1060). To Watson, this unequivocally “taught one of ordinary skill that rivastigmine was susceptible to oxidative degradation and to add an antioxidant to the pharmaceutical composition to prevent it.” (D.I. 311, p. 13).

Novartis’s interpretation of this passage is more nuanced and decisively divergent. According to Dr. Klibanov, the Elmalem article reports the findings of a well-controlled experiment, *i.e.*, one in which any variability that can be eliminated is eliminated. The stated purpose of the Elmalem paper was to compare the effects of three new agents with that of physostigmine. (JTX 159, p. 1059). The simplest way to conduct this experiment would be to prepare aqueous solutions of these four compounds and compare their effects when injected into rabbits. (Tr. 887:20-888:5). The problem with this experiment’s design is physostigmine’s well-documented lack of stability in aqueous solution. (’807 patent, 1:32-34 (“[Physostigmine] is chemically unstable and must be prepared in solution with an antioxidant, and protected from light.”); JTX 148, p. 1266 (“Physostigmine is not stable in aqueous solution.”); JTX 159, p. 1059 (recognizing physostigmine’s “low chemical stability” as a serious disadvantage); Tr. 888:6-9). The instability can be remedied by adding an antioxidant to the physostigmine solution. (Tr. 888:10-11). If, however, the experiment were conducted with physostigmine and an antioxidant injected into one rabbit, and the other three compounds, without an antioxidant, injected into three other rabbits, there would be no way to determine whether any observed difference in the rabbits’ respiratory depression was attributable to the relative chemical activity of the drug or to the presence of the antioxidant. (*Id.* at 888:15-20). The authors of the Elmalem article addressed this concern by adding an antioxidant to all of the drug formulations, including the saline

placebo. (*Id.* at 889:5-14; *id.* at 891:6-11). When read in this context, the statement, “All drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation,” is better understood as a measure to reduce variability than a teaching that RA<sub>7</sub> is subject to oxidative degradation.<sup>20</sup> Indeed, the Elmalem paper did not disclose any stability data for RA<sub>7</sub>. As such, the Elmalem paper would not have motivated a PHOSITA to combine an antioxidant with the transdermal rivastigmine device disclosed by GB '040.

Watson criticizes this “tortuous interpretation” of Elmalem as an attempt to avoid its plain teaching. (D.I. 323, pp. 10-11). First, Dr. Klibanov’s reading of Elmalem requires both that saline be considered a drug and that an antioxidant be added to the saline as a control. (*Id.* at 10). Saline is not mentioned as a drug in the “Drugs” section of the paper, and it does not make sense that “[a]ll drugs were made up freshly in sterile saline” if the authors considered saline itself to be a drug. (JTX 159, p. 1060; D.I. 323, p. 10). The article summary in Elmalem, however, states, “Each drug, RA<sub>6</sub>, (1 mg i.v., 2 mg s.c.) RA<sub>7</sub> (1 or 2 mg i.v.); RA<sub>15</sub> (0.25 or 0.5 mg i.v.), physostigmine (0.05 or 0.1 mg i.v.) or saline (1 ml), was injected simultaneously with morphine (8 mg i.v.) to groups of 6-10 rabbits.” (JTX 159, p. 1059 (punctuation as in original)). The Court accepts Novartis’s argument that this passage indicates the study’s use of the word “drugs” includes RA<sub>6</sub>, RA<sub>7</sub>, RA<sub>15</sub>, physostigmine, and saline, with saline acting as a placebo. (Tr. 886:5-16). It is also logical to conclude that the Elmalem authors added an antioxidant to saline, even though it has no stability issues, because it reduces one of the variables in the experiment. (*Id.* at 888:10-889:2).

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<sup>20</sup> Dr. Klibanov argues that the chemical structure of RA<sub>7</sub> and physostigmine bolsters his reading of Elmalem. Physostigmine is a monomethyl carbamate, whereas RA<sub>7</sub> is a dialkyl carbamate. (D.I. 317, p. 20). The former is unstable in aqueous solution, but the latter is not. (Tr. 879:21-882:21; JTX 147, p. 133; JTX 146, pp. 616-17). A PHOSITA reading Elmalem would appreciate the structural difference between the two drugs and would not have expected RA<sub>7</sub> to oxidatively degrade in aqueous solution. (Tr. 884:4-15). Therefore, the argument goes, it is more likely that the antioxidant was added as a control than to protect RA<sub>7</sub> from oxidative degradation.

Second, Watson contends that under Dr. Klibanov's interpretation, the methodology of Elmalem would not be reproducible because a PHOSITA would not know how much antioxidant to add to the saline solution. (D.I. 323, pp. 10-11). In fact, Dr. Klibanov testified that he did not know how much antioxidant was used in any of the formulations. (Tr. 933:6-12). To Dr. Kibbe, the sentence, "drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite," instructs a PHOSITA to add an amount of antioxidant to each drug formulation that is equivalent to the weight of the drug in that solution. (*Id.* at 664:13-665:13). This tells a PHOSITA how much antioxidant to add to each formulation, but it introduces a new variable because a different amount of antioxidant would be present in each of the injectable formulations.<sup>21</sup> (*Id.* at 891:15-892:10).

This second issue was hotly contested at trial. One seemingly innocuous sentence has given rise to diametrically opposed interpretations, neither of which is without its criticisms. There does not appear to be an objectively "correct" reading; rather both arguments seem logical and are supported by highly qualified experts in the field. Instead of attempting to explain scientifically why one explanation is superior to the other, the better method for resolving this dispute is based on credibility. To that end, the position advanced by Novartis better comports with the Court's understanding of Elmalem, and the Court credits Novartis's accompanying trial testimony as being more credible. Watson has not convinced the Court, by clear and convincing evidence, that Dr. Klibanov's view of the Elmalem article is incorrect. Therefore, the Court accepts Dr. Klibanov's argument on this point, and adopts it as the Court's finding of fact.

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<sup>21</sup> The authors in Elmalem did not use the same concentration of each drug in the experiment.



#### 4. Watson's Other Prior Art References

Watson also relies on U.S. Patent No. 5,580,572 (“the ’572 patent”) and *The Handbook of Pharmaceutical Excipients*, Second Edition (DTX 7) as prior art references that can be combined with GB ’040 to invalidate several of the asserted claims. The ’572 patent discloses a transdermal matrix system for delivering hormones. It teaches the inclusion of an antioxidant, within the concentration ranges claimed in the patents in suit, to stabilize the polymer matrix. (’572 patent, 4:47-52, 16:23; Tr. 648:18-649:18). According to Watson, this would have instructed a PHOSITA that antioxidants could be used to stabilize the polymer in a polymer matrix. (D.I. 311, p. 15). The ’572 patent may indeed teach a PHOSITA that, but Watson has not shown any motivation for the PHOSITA to combine GB ’040 with the ’572 patent. When discussing the transdermal administration of rivastigmine, GB ’040 specifically cites to the hydrophilic polymers described in European Patent Application 0 155 229 (“EP ’229”). (JTX 97, p. 281411). The transdermal devices in EP ’229 do not suggest using an antioxidant. (JTX 109; Tr. 734:17-22). Additionally, rivastigmine is not mentioned in the ’572 patent, and the hormones in the ’572 patent share no chemical or structural similarities with rivastigmine. (Tr. 733:5-11).

The *Handbook of Pharmaceutical Excipients* provides guidance on what antioxidants are suitable for inclusion in pharmaceutical compositions and suggests typical concentration ranges for each antioxidant. (Tr. 631:5-632:21; *see, e.g.*, DTX 7, p. 12). The *Handbook* discloses the antioxidants claimed in the patents in suit, in amounts that fall within the claimed concentration ranges. (Tr. 630:14-644:22). Watson asserts a PHOSITA seeking to add an antioxidant to a transdermal rivastigmine formulation would have referred to the *Handbook*. It is true that the *Handbook* discloses the antioxidants claimed, but absent a reason to believe an antioxidant was

required for a rivastigmine formulation, a PHOSITA would not be motivated to consult the *Handbook*. Because the Court has concluded that nothing in the prior art disclosed rivastigmine's susceptibility to oxidative degradation, a PHOSITA would have no reason to combine the *Handbook*'s teachings with any other prior art reference.

In conclusion, the 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. *See 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. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.”). 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. There can be no motivation to combine prior art references to solve a problem that no one knows exists. *Id.* at 418 (“Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.”). Because I find that a PHOSITA would not have appreciated rivastigmine's susceptibility to oxidative degradation in January 1998, Watson has not proven obviousness by clear and convincing evidence.

### **III. CONCLUSION**

Novartis proved Watson's ANDA products infringe claims 2 and 7 of the '023 patent and claims 3, 7, 13, 16, and 18 of the '031 patent by a preponderance of the evidence. Watson failed to prove by clear and convincing evidence that any of the asserted claims of the '023 or '031 patents were invalid. Novartis should submit an agreed upon form of final judgment within two weeks.