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Paper 69
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVEN PHARMACEUTICALS, INC.,
and MYLAN PHARMACEUTICALS INC.
Petitioner,

v.

NOVARTIS AG and LTS LOHMANN THERAPIE-SYSTEME AG,
Patent Owner.

Case IPR2014-00550[1]
Patent 6,335,031 B1

Before FRANCISCO C. PRATS, ERICA A. FRANKLIN, and CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges.*

FRANKLIN, *Administrative Patent Judge.*

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

[1] Case IPR2015-00268 has been joined with this proceeding.

I. INTRODUCTION

Noven Pharmaceuticals, Inc. ("Noven") filed a petition to institute an *inter partes* review of claims 1–3, 7, 15, 16 and 18 of U.S. Patent No. 6,335,031 B1 (Ex. 1001, "the '031 patent"). Paper 1 ("Petition" or "Pet.").[2] Novartis AG and LTS Lohmann Therapie-Systeme AG (collectively, "Patent Owner") filed a Preliminary Response to the Petition. Paper 7 ("Prelim. Resp."). In an Institution Decision (Paper 10), an *inter partes* review of claims 1–3, 7, 15, 16 and 18 was instituted.

After the Institution Decision, Mylan Pharmaceuticals Inc. ("Mylan") timely filed a separate petition to institute an *inter partes* review of claims 1–3, 7, 15, 16 and 18 of the '031 patent based on identical grounds as presented in Noven's Petition. Case IPR2015-00268, Paper 1. At the same time, Mylan filed a Motion for Joinder with the instituted case. *Id*., Paper 3. Patent Owner filed an Opposition to the Motion for Joinder and a Patent Owner's Preliminary Response. Papers 10, 13. In an Institution Decision, an *inter partes* review of claims 1–3, 7, 15, 16 and 18 was instituted in IPR2015-00268, the Motion for Joinder was granted, and the proceeding in IPR2015-00268 was terminated. Paper 17. Therefore, in the instant *inter partes* review, Noven and Mylan are, collectively, the "Petitioner."

In the instant *inter partes* review, Patent Owner filed a Response to the Petition. Paper 25 ("Patent Owner Response" or "PO Resp."). Petitioner filed a Reply. Papers 31 and 32 ("Pet. Reply").[3] Patent Owner filed motions for observations on the cross-examinations of two deposed declarant

[2] Pursuant to an order, Paper 27, granting an unopposed motion by Petitioner, Paper 21, Petitioner filed a Corrected Petition, Paper 37, to correct certain clerical and typographical errors in the list of exhibits.
[3] Paper 31 was filed under seal and Paper 32 is a redacted public version.

witnesses. Papers 42, 43, 44.[4] Petitioner filed responses to the motions. Papers 52, 53 and 54.[5] Additionally, Petitioner filed a motion to exclude a number of Patent Owner's exhibits. Paper 47. Patent Owner filed an opposition to the motion. Paper 49. Petitioner responds to the opposition in a Reply in Support of the Motion to Exclude. Paper 57. On June 2, 2015, the parties presented arguments at an oral hearing. Paper 67, ("Tr.").[6]

The Board has jurisdiction under 35 U.S.C. § 6(c). In this Final Written Decision, issued pursuant to 35 U.S. C. § 318(a) and 37 C.F.R. § 42.73, we determine Petitioner has shown by a preponderance of the evidence that challenged claims 1–3, 7, 15, 16 and 18 are unpatentable.

A. Related Proceedings

According to Petitioner and Patent Owner, the '031 patent was involved in various district court actions, including two actions involving the parties to this proceeding, titled: *Novartis Pharm. Corp. v. Noven Pharm. Inc.*, 1:13-cv-00527 (D. Del.); and *Novartis Pharm. Corp. v. Noven Pharm. Inc.*, 1:14-cv-00111 (D. Del.). Pet. 1–2; Paper 6 at 2. Those cases were consolidated, and on August 31, 2015, the United States District Court for

[4] Patent Owner filed a Confidential Motion for Observations on Cross-Examination of Dr. Agis Kydonieus under seal, Paper 42, and a redacted, "Non-Confidential" public version, Paper 43. Paper 44 is Patent Owner's Motion for Observation on Cross-Examination of Dr. Christian Schöneich.
[5] Petitioner filed a Response to Patent Owner's Confidential Motion for Observations on Cross-Examination of Dr. Kydonieus under seal, Paper 54, and a redacted, "Non-Confidential" public version, Paper 53. Paper 52 is Petitioner's Response to Patent Owner's Motion for Observation on Cross-Examination of Dr. Schöneich.
[6] Patent Owner filed Objections to Petitioner's Demonstrative Exhibits. Paper 63. In this Final Written Decision, we have not considered any arguments presented in the demonstrative exhibits that were not presented previously and/or are not supported by the record.

the District of Delaware issued a decision finding that Noven failed to prove by clear and convincing evidence that claims 7 and 16 of the '031 patent are invalid as obvious or invalid under the obviousness-type double patenting doctrine. *Novartis Pharm. Corp. v. Noven Pharm., Inc.*, —F. Supp. 3d—, Civ. Nos. 13-527-RGA, 14-111-RGA, 2015 WL 5121157 (D. Del. Aug. 31, 2015) ("*Noven*"). Although in *Noven*, the District Court considered the same prior art presented in this *inter partes* review, the District Court's opinion is not binding in this proceeding. We have independently analyzed the prior art in view of the record evidence as a whole, including the knowledge of a person of ordinary skill in the art. Our findings and conclusions differ from the District Court in that we have accorded persuasive weight to the testimony of Petitioner's declarants. Moreover, the petitioner in an *inter partes* review proves unpatentability by a preponderance of the evidence (*see* 35 U.S.C. § 316(e)) rather than by clear and convincing evidence, as required in district court litigation.

In another case involving Novartis, but not Noven or Mylan, the same District Court held that claims 3, 7, 13, 16 and 18 of the '031 patent are not invalid as obvious. *Novartis Pharms. Corp. v. Par Pharm., Inc.*, 48 F. Supp. 3d 733 (D. Del. 2014). The Court of Appeals for the Federal Circuit affirmed that District Court decision upholding the validity of the '031 patent. *Novartis Pharm. Corp. v. Watson Labs., Inc.*, — F. App'x —, Nos. 2014-1799 et al., 2015 WL 2403308 at *5–8 (Fed. Cir. May 21, 2015) ("*Watson*"). The Federal Circuit's *Watson* decision does not control here because Noven has presented additional prior art and declaratory evidence that was not before the Court in *Watson*. Moreover, as discussed previously, in an *inter partes* review, a petitioner's burden of proving unpatentability is

by a preponderance of the evidence rather than by clear and convincing evidence. Thus, while we have considered the Federal Circuit's decision, we have independently analyzed patentability of the challenged claims based on the evidence and standards that are applicable to this proceeding.

A final decision in an *inter partes* review of claims of a related patent, U.S. Patent No. 6,316,023 B1, has been entered concurrently with this decision. IPR2014-00549, Paper 69.

B. The '031 Patent (Ex. 1001)

The '031 patent is directed to a pharmaceutical composition comprising (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methylphenyl carbamate ("compound A"; "rivastigmine"; "S-enantiomer of RA_7") in the form of a free base or acid addition salt, along with an antioxidant, and a diluent or carrier. Ex. 1001, 1:7–47. "Compound A is useful in inhibiting acetylcholinesterase in the central nervous system, e.g. for the treatment of Alzheimer's disease." *Id*. at 1:14–16. A transdermal composition comprising compound A in the form of a free base or acid addition salt, two polymers, and a plasticizer is disclosed in the prior art. *Id*. at 1:17–21. The inventors of the '031 patent explained that the composition of the prior art "is susceptible to degradation, particularly in the presence of oxygen." *Id*. at 1:22–24. The '031 patent states:

> The present applicant has found that stable pharmaceutical compositions comprising compound A can now be obtained, which show insignificant degradation of compound A over a prolonged time period, e.g. 2 years, as indicated by standard tests, e.g. stress tests.
>
> In one aspect, the invention provides a pharmaceutical composition comprising Compound A in free base or acid addition salt form and an anti-oxidant.

> The pharmaceutical compositions of the present invention show a reduction in degradation by-products in stress stability tests.

Id. at 1:29–39.

The ’031 patent discloses that an effective stabilization effect is achieved “when the antioxidant is selected from tocopherol, esters thereof, e.g. tocopherol acetate, ascorbyl palmitate, ascorbic acid, butylhydroxytoluene, butylhydroxyanisone or propyl gallate, preferably α-tocopherol or ascorbyl palmitate.” *Id*. at 4:11–16. “The antioxidant may be conveniently present in an amount of from about 0.01 to about 0.5% . . . by weight based on the total weight of the pharmaceutical composition.” *Id*. at 4:16–19.

Additionally, the ’031 patent teaches that “[t]he pharmaceutical compositions of the invention may contain high amounts of compound A, e.g. from 1 to 40% by weight.” *Id*. at 1:40–42.

C. Illustrative Claims

Claims 1, 7 and 15 of the ’031 patent are illustrative of the claims at issue:

> 1. 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.

Ex. 1001, 8:14–21.

> 7. A transdermal device comprising a pharmaceutical composition as defined by claim 1, wherein the pharmaceutical composition is supported by a substrate.

Id. at 8:49–51.

> 15. 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 anti-oxidant effective to stabilize Compound A from degradation.

Id. at 9:10–15.

D. The Prior Art

Enz	UK Patent Application GB 2,203,040 A, published Oct. 12, 1988 ("Enz")	Ex. 1002
Handbook	HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (A. Wade & P.J. Weller eds., 2d ed. 1994) ("the Handbook")	Ex. 1003
Sasaki	JP Patent Application 59-184121, published Oct. 19, 1984 ("Sasaki")	Ex. 1005
Ebert	WO 95/24172, published Sept. 14, 1995 ("Ebert")	Ex. 1006
Rosin	US 4,948,807, issued Aug. 14, 1990 ("Rosin")	Ex. 1008
Elmalem	*Antagonism of Morphine-Induced Respiratory Depression by Novel Anticholinesterase Agents*, 30 NEUROPHARMACOLOGY 1059–64 (1991) ("Elmalem")	Ex. 1009

Petitioner also relies on two declarations of Dr. Agis Kydonieus, Ex. 1010; Ex. 1031, and two declarations of Dr. Christian Schöneich, Ex. 1011; Ex. 1032. Patent Owner relies on the declaration of Dr. Alexander

M. Klibanov, Ex. 2012.

E. The Instituted Grounds of Unpatentability

Trial was instituted for claims 1–3, 7, 15, 16 and 18 of the '031 patent on the following grounds:

Reference(s)	Basis	Claims
Enz, the Handbook, Rosin, Elmalem, and Ebert	§ 103(a)	1, 2, 7, 15 and 18
Enz, the Handbook, Rosin, and Ebert	§ 103(a)	3 and 16
Enz and Sasaki	§ 103(a)	1–3, 7, 15, 16 and 18

III. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner asserts that the claim term "stabilizing" means "reducing degradation." Pet. 8 (citing Ex. 1001, 4:5–30). Patent Owner proposes that

this term means "significantly reducing degradation of Compound A over a prolonged period of time." Prelim. Resp. 12.[7]

The term "stabilizing" is recited in claim 15, i.e., "A method of stabilizing . . . Compound A." The Specification does not define this term expressly. The Specification states, "stable pharmaceutical compositions comprising compound A can now be obtained, which show insignificant degradation of compound A over a prolonged time period, e.g. 2 years, as indicated by standard tests, e.g. stress tests." Ex. 1001, 1:29–33. The Specification discloses that the addition of tocopherol to a composition containing compound A resulted in a smaller percentage of degradation products as compared to compositions not containing tocopherol. *Id.* at 4:20–30. The percentages of degradation products were determined using two or three month stress tests. *Id*. at 4:20–30.

Based on the evidence and arguments, we determine that Petitioner's interpretation is the broadest reasonable construction in light of the Specification. Although the Specification describes obtaining stable compositions which show insignificant degradation of compound A over a prolonged time period and using a two- or three-month stress test to determine a reduction in degradation, neither those disclosures nor the language of claim 15 limit "stabilizing" to refer only to a reduction in degradation that is significant, or over a "prolonged" period of time, as urged by Patent Owner. *See Home Diagnostics, Inc., v. Lifescan, Inc*., 381 F.3d 1352, 1358 (Fed. Cir. 2004)(discussing a specification description that

[7] Patent Owner does not revisit the issue of claim construction for any term in the Patent Owner Response.

does not amount to the kind of clear disavowal that supports importing an unclaimed limitation from the specification).

Similarly, Petitioner asserts that the claim phrase "an amount of antioxidant effective to stabilize Compound A from degradation" means "an amount of antioxidant that reduces the oxidative degradation of Compound A." Pet. 8 (citing Ex. 1001, 1:29–33). Patent Owner proposes that this term means "an amount of antioxidant that will significantly reduce degradation of Compound A over a prolonged period of time." Prelim. Resp. 8–9. On the current record, we agree that Petitioner's interpretation is the broadest reasonable construction in light of the Specification for the same reason discussed regarding the term "stabilizing."

The parties agree that the term "(S)-N-ethyl-3-[(1-dimethylamino) ethyl]-N-methylphenyl carbamate" refers to rivastigmine, i.e., the S-enantiomer of a racemic mixture known as RA_7, i.e., N-ethyl-3-{(1-dimethylamino)ethyl}-N-methyl-phenyl-carbamate HCl. Pet. 8–9; Prelim. Resp. 13. Upon consideration of the record, we adopt that agreed-upon construction as it is consistent with the plain and ordinary meaning in the context of the Specification.

Based on our analysis, we determine that no express claim construction is necessary for any remaining claim term.

B. Level of Skill in the Art

Petitioner asserts that the person of ordinary skill in the art at the time of the invention would have: (a) been "a chemist, chemical engineer, polymer chemist or pharmaceutical chemist working to develop pharmaceutical formulations, including transdermal drug deliver systems;" (b) been familiar with testing that accompanies the development of any

pharmaceutical formulation, including testing efficacy and stability; (c) been familiar with excipients typically employed in pharmaceutical formulations, including transdermal devices; and (d) had knowledge of organic chemistry and been able to predict the physical properties of a compound based on its chemical structure. Pet. 5–6 (citing Decl. of Dr. Kydonieus, Ex. 1010 ¶ 9). Patent Owner does not provide a statement in the Preliminary Response or Patent Owner's Response asserting a description of the level of ordinary skill in the art.

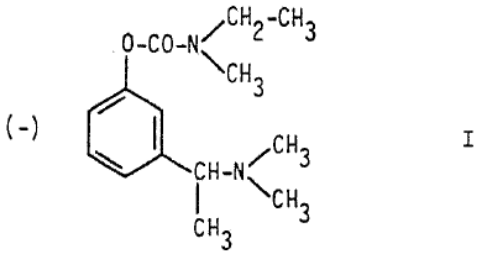
The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) and *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)). Based on our consideration of the record, we find that the evidence supports the Petitioner's description of the level of ordinary skill in the art, with the following modification to portion (d) to read as follows: had knowledge of organic chemistry and been able to *analyze* and recognize certain characteristics of a compound based on its chemical structure. As explained by Petitioner's declarants: the ability to predict reactivity based on functional group properties is a foundation of organic chemistry, Decl. of Dr. Schöneich, Ex. 1032 ¶¶ 22–25, and a person of ordinary skill in the art would have understood that the presence of particular functional groups in a molecule has consequences, Decl. of Dr. Kydonieus, Ex. 1031 ¶¶ 28–29; Ex. 1032 ¶¶ 7–13, 24–25.

C. Obviousness of Claims 1–3, 7, 15, 16 and 18 over Enz (Ex. 1002) and Sasaki (Ex. 1005)

Petitioner contends that claims 1–3, 7, 15, 16 and 18 would have been obvious to a person of ordinary skill in the art at the time the invention was made over the combination of Enz and Sasaki. Pet. 43–51. Patent Owner disagrees. PO Resp. 9–22, 40–44.

1. Enz

Enz discloses compositions for systemic transdermal administration containing (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl carbamate of formula I, reproduced below:



I

Ex. 1002, 2.

The compound of formula I may be in free base or acid addition salt form. *Id*. Enz explains that the racemic mixture (±)-N-ethyl-3-[1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate in the form of its hydrochloride is known as RA_7. *Id*. at 3. Enz teaches that (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate in free base may be prepared from the racemate by separation of the enantiomers in accordance with known methods. *Id*. The acid addition salts may be prepared from the free base according to a known manner. *Id*. Enz teaches that Compound A, the compound of formula I in the form of its hydrogen tartrate, is "slightly superior than" the racemic mixture. *Id*. at 6.

Additionally, Enz discloses providing "a pharmaceutical composition

comprising a compound according to the invention in association with at least one pharmaceutical carrier or diluent." *Id.* at 11. In Example 2, Enz discloses a preparation of a transdermal composition comprising 20% of compound A, 30% of a hydrophilic polymer, e.g., Eudragit® E 100, 44% of a non-swellable acrylate polymer, e.g., Durotack® 280-2416, and 6% of a plasticizer, e.g., Brij® 97. *Id*. at 20. The composition is spread on top of an aluminized foil to produce a film that is allowed to dry. *Id*. Thereafter, the aluminum foil is cut into patches. *Id*.

Enz discloses a daily dosage in the range from about 0.1 to about 25 mg, e.g., 0.1 to about 5 mg, of a compound according to the invention. *Id*. at 10.

2. Sasaki

Sasaki discloses an acrylic adhesive plaster comprising tocopherol and a drug. Ex. 1005, 1. Sasaki teaches that the therapeutic effect of a preparation comprising a drug blended with a plaster comprising an acrylic adhesive substance tends to be greatly reduced due to the breakdown and dissipation of the drug when the adhesive substance is stored for a long time. *Id*. at 1. Sasaki explains that breakdown of the drug in such a composition occurs especially when the drug is a phenolic hydroxyl group-containing compound, an amine compound, or the like. *Id*. Sasaki teaches that if a tocopherol, an antioxidant, is blended in a plaster comprising a drug and an acrylic adhesive substance, "the drug will be stably present without breaking down." *Id*. at 2.

Additionally, Sasaki discloses the amount of tocopherol blended is on the order of 0.005 to 5 weight percent, and preferably on the order of 0.05 to 1 weight percent, relative to the acrylic adhesive. *Id*. Further, Sasaki

teaches that there are no particular limits on the drug which is blended in the plaster of the present invention, so long as the drug can be formed into an adhesive patch preparation and administered to a subject in such a dosage form. *Id*. at 2–3.

2. Analysis

a. Claims 1 and 7

Petitioner asserts that Enz teaches a composition that meets every limitation of claims 1 and 7, except the addition of an antioxidant. Pet. 43–44. Specifically, Petitioner asserts that Enz discloses in Example 2 a pharmaceutical composition, e.g., a transdermal device, comprising the hydrogen tartrate salt of rivastigmine, i.e., (S)-N-ethyl-3-[(1-dimethylamino)ethyl]-N-methyl-phenyl-carbamate, Eudragit® E 100 (a hydrophilic polymer) and Durotack® 280-2416 (an acrylic adhesive), i.e., a diluent or carrier, and Brij® 97 (a plasticizer). *Id*. at 30–31. Petitioner asserts also that Enz discloses a daily dosage of from about 0.1 to about 25 mg of rivastigmine, i.e., a therapeutically effective amount of Compound A. *Id*. at 31 (citing Ex. 1002, 10). Patent Owner does not dispute that Enz discloses those limitations of claims 1 and 7. PO Resp. 21–22.

Accordingly, our analysis turns to whether a preponderance of the evidence establishes, based on the teachings of Enz and Sasaki, that along with the knowledge generally available to one of ordinary skill in the art, it would have been obvious to a person of ordinary skill in the art at the time of the invention who endeavored to formulate rivastigmine into a transdermal patch, as taught by Enz, to have added an antioxidant as taught by Sasaki.

Petitioner, relying on the declaration testimony of Dr. Kydonieus,

asserts that Sasaki provides a person of ordinary skill in the art a reasonable expectation that the rivastigmine transdermal patch formulation taught by Enz would be unstable during long-term storage of two to three years. Pet. 46–47 (citing Ex. 1010 ¶ 85). Specifically, Petitioner asserts that Enz serves as a starting point for formulating a rivastigmine transdermal patch, but does not provide stability data or any discussion of susceptibility to oxidation, for the product. *Id*. at 46. Relying upon the declaration testimony of Dr. Kydonieus, Petitioner asserts that those having skill in the art would have "strive[d] to develop stable pharmaceutical products with a commercially viable shelf life." *Id*. at 47 (quoting Ex. 1010 ¶ 86). In furtherance of that goal, according to Petitioner and Dr. Kydonieus, "one of the first steps a person of ordinary skill in the art would have taken when formulating a drug is to investigate the stability of the active component." *Id*. at 45–46 (citing Ex. 1010 ¶ 83).

Petitioner asserts that Sasaki informs that investigation. Pet. 46–47. In particular, Petitioner asserts that Sasaki teaches that compounds having an amino group can undergo oxidative decomposition over the shelf life of the product when the product comprises an acrylic adhesive. *Id*. at 46 (citing Ex. 1005, 1; Ex. 1010 ¶ 85). According to Petitioner and Dr. Kydonieus, based on that teaching of Sasaki, a person of ordinary skill in the art would have expected Enz's transdermal patch to be unstable during long-term storage because it comprised a drug having an amino group, i.e., rivastigmine, *see* Ex. 1011 ¶ 12, and it was formulated with an acrylic adhesive, i.e., Durotack® 280-2416. Pet. 46 (citing Ex. 1010 ¶ 85).

Petitioner asserts further that the person of ordinary skill would have been motivated to add an antioxidant to Enz's rivastigmine transdermal

composition with a reasonable expectation of maintaining the stability of the patch during long-term storage, as this is the precise solution disclosed by Sasaki. *Id*. at 48. Moreover, at the time of the invention, antioxidants were commonly included in pharmaceutical products, including transdermal devices, to protect the drug and/or excipients from oxidative degradation. *Id*. at 47 (citing Ex. 1010 ¶ 86; Ex. 1011 ¶ 50). Additionally, Petitioner asserts that the person of skill in the art would have been motivated to add the amount of antioxidant disclosed by Sasaki, which amount meets the requirements of claims 1 and 7 of the '031 patent. *Id*. at 48.

Patent Owner contends that Sasaki does not teach or suggest any oxidative degradation problem for rivastigmine, and, therefore, a person of ordinary skill in the art would not have been motivated to include an antioxidant in the rivastigmine transdermal formulation disclosed by Enz. PO Resp. 43. In particular, Patent Owner challenges Sasaki by asserting that it does not mention rivastigmine and discloses only two exemplary amine-containing compounds in transdermal formulations. *Id*. at 40–41.

According to Patent Owner, and Patent Owner's declarant, Dr. Klibanov, Sasaki's disclosure of only two amine-containing compounds "would not have taught or suggested to a [person of ordinary skill in the art] as of 1998 that all amine-containing compounds break down in any acrylic adhesive." *Id*. at 41 (citing Ex. 2012 ¶¶ 156–158). Specifically, Patent Owner asserts that a person of skill in the art would not reasonably have predicted from the presence of an amine group in rivastigmine's structure that rivastigmine would oxidatively degrade under pharmaceutically relevant

conditions.[8] *Id*. at 41–42 (citing Ex. 2012 ¶¶ 130–137, 150, 156.). Rather, Patent Owner asserts, only "the structure of the molecule as a whole matters to its chemical stability" and "whether a compound will degrade in a particular formulation cannot be predicted in advance of testing." *Id*. at 42 (citing Ex. 2012 ¶¶ 130–137, 156). According to Patent Owner, both of Petitioner's declarants, Dr. Kydonieus and Dr. Schöneich, agree that it cannot be predicted whether a compound will degrade in a particular formulation in advance of testing, and that Dr. Kydonieus "admitted that he could not be certain whether rivastigmine would necessarily undergo oxidative degradation in any acrylic adhesive." *Id.* (citing Ex. 1025, 95:24–96:18, 232:6–13, 258:8–13, 283:12–284:19; Ex. 1029, 53:10–17).

Additionally, Patent Owner asserts that contrary to Sasaki's teaching, "there were numerous amine-containing drug compounds not reported to contain antioxidants in their commercial formulations–including one in a transdermal formulation using acrylic adhesives." PO Resp. 42 (citing Ex. 2012 ¶¶ 133–135, 157; Ex. 2022, 884). Patent Owner asserts also that Enz contradicts Sasaki by not teaching or suggesting that rivastigmine will break down in its transdermal formulation comprising an acrylic adhesive. *Id*. at 43 (citing Ex. 2012 ¶ 158).

After considering the record as a whole, we agree with Petitioner that a person of ordinary skill in the art would have been motivated to add an antioxidant to the transdermal rivastigmine formulation disclosed by Enz. Sasaki teaches that if a drug is blended with a plaster comprising an acrylic

[8] At the oral hearing, Patent Owner explained that it uses the phrase "pharmaceutically relevant conditions" as referring to "the types of conditions that the drug would encounter during formulation and storage." Tr. 60:14–17.

acid adhesive, there is a tendency for the therapeutic effect of the preparation to be greatly reduced due to the breakdown and dissipation of the drug. Ex. 1005, 1. Sasaki explained that this breakdown occurs "especially" when the drug is a phenolic hydroxyl group containing compound, an amine compound, or the like. *Id*. Based on those teachings by Sasaki and the knowledge in the art that rivastigmine is a compound comprising an amino group, Ex. 1011 ¶ 12, it would have been reasonable for a person of ordinary skill in the art to have expected Enz's formulation comprising rivastigmine and an acrylic polymer adhesive, i.e., Durotack® 280-2416, to be unstable during long-term storage.

That rationale for applying Sasaki's teaching to the rivastigmine transdermal formulation disclosed by Enz is not diminished by Patent Owner's assertion that Sasaki did not mention expressly rivastigmine or provide more than two exemplary amine compounds. The applicability of Sasaki's teaching regarding the stability of amine compounds formulated with acrylic adhesives is not limited to its examples. *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Moreover, a motivation to combine teachings need not be expressly stated in any prior art reference. *In re Kahn*, 441 F.3d 977, 987. (Fed. Cir. 2006). Rather, as here, the reason to combine the teachings need only be an articulated with some rational underpinning to support a conclusion of obviousness. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 418 (2007) (citing *Kahn*, 441 F.3d at 988).

We determine also that Patent Owner's argument does not overcome Petitioner's showing that, in view of Sasaki's teaching, a person of ordinary skill in the art would have been able to reasonably predict "in advance of testing" that rivastigmine would degrade when formulated with an acrylic

adhesive. PO Resp. 42. In support of its contention to the contrary, Patent Owner relies upon the declaration of Dr. Klibanov. On this point, Dr. Klibanov discusses five exemplary pharmaceutical compounds containing an amine, but not reported to contain an antioxidant in the commercial formulation. Ex. 2012 ¶ 133 (referring to ampicillin, hydroxyzine, meclizine, mirtazapine, and benzquiamide). However, as acknowledged by Dr. Klibanov, *id.* ¶ 134, none of those five examples referred to a transdermal formulation including an acrylic adhesive, so as to make them relevant to Sasaki's disclosure.

Dr. Klibanov discusses next two compounds containing an amine and formulated into commercial transdermal products that he asserts were not reported to contain antioxidants prior to the claimed invention. *Id*. ¶ 135 (referring to Duragesic® comprising fentanyl and Trans-derm Scop® comprising scopolamine). Referring to the Physician's Desk Reference ("PDR"), Dr. Klibanov takes the position that the commercial formulations for transdermal devices comprising those compounds are not reported to undergo oxidative degradation. *Id*. ¶¶ 135–138 (citing, e.g., the 1997 PDR, Ex. 2022, 890–91, 1336–40). However, Dr. Klibanov has not described those formulations as including an acrylic adhesive, so as to make them relevant to Sasaki's disclosure.

Dr. Klibanov discusses also a nicotine patch, Habitrol®, that was commercially available at the time of the invention, along with three other amine containing compounds formulated as transdermal products that were commercially available after 1998, each of which were formulated with an acrylate adhesive and not reported to include an antioxidant. Ex. 2012 ¶ 157 (citing Ex. 2022, 884). However, neither Dr. Klibanov nor Patent Owner

has identified any statement in the PDR describing the stability or shelf-life of any of those transdermal formulations. Nor has Dr. Klibanov discussed in the declaration whether those commercial formulations address drug stability by some means other than adding an antioxidant. Indeed, in his deposition testimony, Dr. Klibanov acknowledged that conclusions regarding a drug's susceptibility to oxidation cannot be made based upon its formulation being reported not to include an antioxidant, because other means of preventing oxidation may have been employed. Ex. 1026, 247:9–249:6; Pet. Reply 9; Ex. 1032 ¶ 42. Thus, we find that Dr. Klibanov's declaration testimony challenging the legitimacy of Sasaki's teaching not entitled to persuasive weight as it is unsupported by evidence and instead is based upon an assumption drawn from an incomplete analysis of the asserted evidence. *See Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997) (no requirement to credit unsupported assertions of an expert witness).

Similarly, we remain persuaded by Petitioner's showing, despite Patent Owner's assertion that Enz contradicts Sasaki by not teaching or suggesting that its formulation of rivastigmine and an acrylic adhesive would undergo oxidative degradation. PO Resp. 43. Based upon an observation that Enz does not discuss oxidative stability or degradation, Dr. Klibanov concludes that "Enz teaches a transdermal device for an amine-containing compound and an acrylic adhesive that does not undergo oxidative degradation and does not require an antioxidant." Ex. 2012 ¶ 158. We find, once again, that Dr. Klibanov's testimony is not entitled to persuasive weight as it is not supported by the asserted evidence. Enz does not address the stability of its formulation. Indeed, as acknowledged by

Patent Owner, "Enz moreover does not teach or suggest anything about the oxidative degradation of rivastigmine." PO Resp. 21–22. Dr. Klibanov has not explained or provided evidence that one of ordinary skill in the art would have reasonably drawn an inference about the stability or oxidative degradation of a preparation from a disclosure that did not address "anything" about the topic. *See In re Preda*, 401 F.2d 825, 826 (CCPA 1968) (inferences drawn from scope and content of prior art must be ones that one of skill in the art would reasonably be expected to draw). As Petitioner explained, Enz provides a "starting point" for a rivastigmine transdermal formulation. As the starting point, we agree with Petitioner that a skilled artisan who endeavored to prepare Enz's formulation as a commercial product would have investigated its stability and taken steps to ensure a viable shelf life.

Moreover, we disagree with Patent Owner's assertion that Petitioner's declarants, Dr. Kydonieus and Dr. Schöneich, agree that it cannot be reasonably predicted whether a compound will be susceptible to degradation in a particular formulation in advance of testing. More precisely, we find that the testimony of Dr. Kydonieus and Dr. Schöneich relied upon by Patent Owner explains that susceptibility to oxidative degradation can be reasonably predicted from a compound's molecular structure, whereas, whether and to what extent that expected degradation *actually* occurs needs to be shown experimentally. *See, e.g.*, Ex. 1025, 258:8–13 (testimony of Dr. Kydonieus)[9] and 96:13–18 (testimony of Dr. Schöneich). Indeed, as Patent Owner acknowledges, Dr. Kydonieus explained that without such testing "he

[9] *See also* Ex. 1031 ¶ 54 (Dr. Kydonieus explaining that a person of ordinary skill in the art "would not have understood the susceptibility of rivastigmine to oxidative degradation to vary based on method of drug delivery").

could not be certain whether rivastigmine would necessarily undergo oxidative degradation in any acrylic adhesive." PO Resp. 42 (citing Ex. 1025, 283:12–21.

In other words, Dr. Kydonieus and Dr. Schöneich agree that although a skilled artisan may not be able to predict *absolutely* whether a compound will degrade oxidatively based on its structure alone, a reasonable prediction can be made regarding its potential and susceptibility to do so. In an obviousness analysis, absolute predictability is not the standard. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Rather, the proper inquiry focuses on reasonable expectations that a skilled artisan would gain from the teachings or suggestions of the combined prior art. *Id*. at 903–04.[10] Patent Owner and its declarant, Dr. Klibanov, have mistakenly disregarded the significance of the suggestion provided by the combined prior art that a compound having an amine group and formulated with an acrylic plaster is susceptible to oxidative degradation. It is this susceptibility, i.e., predicted potential for oxidative degradation, that provides the skilled artisan with a reasonable expectation that the formulation will oxidatively degrade, and the motivation to address that problem by employing a means known to avoid that problem, such as adding an antioxidant, as taught by Sasaki.

Thus, contrary to Patent Owner's contention, PO Resp. 5, this case can be distinguished from the situation in *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1353 (Fed. Cir. 2013) because here, the problem regarding oxidative degradation of certain compounds formulated in acrylic adhesives was "recognized and solved" by the prior art. Patent Owner

[10] As Patent Owner's counsel acknowledged at the hearing, "Absolute predictability is not the standard. The standard is whether it was known or reasonably suggested in the prior art." Tr. 54:4–6.

asserts also that "as in *Leo*, the invention of the '031 [p]atent did not appear until a decade after the 1988 publication of Petitioner's primary art reference, Enz." PO Resp. 8. However, unlike in *Leo*, here, a preponderance of the evidence supports finding that a person of ordinary skill in the art would have understood the addition of an antioxidant to Enz, i.e., the invention of the '031 patent, was suggested by the prior art. Moreover, absent a long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness. *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1324–25 (Fed. Cir. 2004).

Similarly, contrary to Patent Owner's contention, PO Resp. 5, this case is also distinguishable from *In re Omeprazole Patent Litig*ation, 536 F.3d 1361, 1380–81 (Fed. Cir. 2008) because here, the prior art suggested the need to stabilize formulations such as that disclosed by Enz.

Based on the foregoing discussion and the record as a whole, we find that a person of ordinary skill in the art would have predicted that the transdermal formulation disclosed by Enz was susceptible to oxidative degradation, based on an application of Sasaki's teachings, and would have been motivated to add an antioxidant to the formulation with a reasonable expectation of successfully avoiding that predicted degradation. Accordingly, we conclude that the preponderance of the evidence demonstrates that the combined prior art renders obvious the inventions of claims 1 and 7 of the '031 patent.

b. Claim 2

Claim 2 depends from claim 1, further requiring the pharmaceutical composition of claim 1 to contain "1 to 40% by weight of Compound A."

Ex. 1001, 8:22–24. Petitioner asserts that the combination of Enz and Sasaki renders this further limitation of claim 2 obvious. Pet. 48–49. In Example 2, Enz discloses a preparation of a transdermal composition comprising 20% by weight of compound A, which falls within the range required by claim 2. Ex. 1002, 20. Patent Owner does not raise separate arguments addressing the limitations of dependent claim 2.

Based on the record as a whole, we find that Petitioner has established persuasively that the preponderance of the evidence shows that claim 2 would have been obvious over Enz and Sasaki to a person of ordinary skill in the art at the time of the invention.

c. Claim 15

Independent claim 15 is directed to a method comprising combining Compound A with "an amount of anti-oxidant effective to stabilize Compound A from degradation." Ex. 1001, 9:10–15. Petitioner asserts that a person of ordinary skill in the art would have been motivated to combine rivastigmine with an antioxidant for the reasons discussed regarding claim 1. Pet. 49. According to Petitioner, adding an antioxidant, according to Sasaki's disclosure, to the composition of Enz would have resulted in the method of claim 15. *Id*. Patent Owner does not raise separate arguments addressing claim 15.

We have interpreted the claim term "stabilizing" to mean "reducing degradation," and the claim phrase "an amount of antioxidant effective to stabilize Compound A from degradation" to mean "an amount of antioxidant that reduces oxidative degradation of Compound A." Based on these constructions and the record as a whole, we find that Petitioner has established persuasively that the preponderance of the evidence shows that

claim 15 would have been obvious over Enz and Sasaki to a person of ordinary skill in the art at the time of the invention.

d. Claim 18

Claim 18 depends from claim 15 and further recites that "the anti-oxidant is present in an amount of from about 0.01 to about 0.5% by weight based on the weight of the composition." Ex. 1001, 10:6–8. Petitioner asserts that the combination of Enz and Sasaki renders this claim obvious. Pet. 49–50. Sasaki disclosed using an amount of tocopherol on the order of 0.005 to 5 weight percent, and preferably on the order of 0.05 to 1 weight percent relative to the acrylic adhesive. Ex. 1005, 2. Enz discloses that its patch contains 44% acrylic adhesive by weight. Ex. 1002, 20. Therefore, according to Petitioner, a person of ordinary skill in the art at the time of the invention "would have been motivated to add tocopherol in a range of 0.0022–2.2 wt. % relative to the total weight of the pharmaceutical composition in Enz," Pet. 50 (citing Ex. 1010 ¶ 90), which encompasses the range recited in claim 18. Patent Owner does not raise separate arguments addressing claim 18.

Based on the record as a whole, we find that Petitioner has established persuasively that the preponderance of the evidence shows that claim 18 would have been obvious over Enz and Sasaki to a person of ordinary skill in the art at the time of the invention.

e. Claims 3 and 16

Claim 3 depends from claim 1 and claim 16 depends from claim 15. Claims 3 and 16 require that "the anti-oxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate." Ex. 1001, 8:25–28, 10:1–3. Petitioner asserts that the combination of Enz

and Sasaki renders claims 3 and 16 obvious, as both claims allow the selection of tocopherol as the anti-oxidant, which is the same anti-oxidant that is expressly taught in Sasaki. Pet. 50–51. Patent Owner does not raise separate arguments addressing claims 3 and 16.

Based on the record as a whole, we find that Petitioner has established persuasively that the preponderance of the evidence shows that claims 3 and 16 would have been obvious over Enz and Sasaki to a person of ordinary skill in the art at the time of the invention.

Accordingly, for the reasons discussed, we conclude that Petitioner has established by a preponderance of the evidence that claims 1–3, 7, 15, 16 and 18 are rendered obvious by the combination of Enz and Sasaki.

D. Obviousness of Claims 1, 2, 7, 15 and 18 over Enz (Ex. 1002), the Handbook (Ex. 1003), Rosin (Ex. 1008), Elmalem (Ex. 1009) and Ebert (Ex. 1006)

Petitioner contends that claims 1, 2, 7, 15 and 18 are unpatentable over the combination of Enz and the Handbook, optionally in view of Rosin and/or Elmalem and/or Ebert. Pet. 30–41. We incorporate here our earlier findings and discussion regarding the disclosure of Enz.

1. The Handbook

The Handbook lists pharmaceutical excipients and provides a description of each excipient, including nonproprietary and chemical names, structural formula, functional category, applications in pharmaceutical formulation or technology, and in some cases, the normal usage concentration range. Ex. 1003, 5. The Handbook identifies several excipients as antioxidants, including alpha tocopherol, normally used in the concentration range of 0.001–0.05%. *Id*. at 5–7.

2. Rosin

Rosin describes "a need to provide new carbamate derivatives which show greater chemical stability than physostigmine." Ex. 1008, 3:36–38. Rosin discloses phenyl carbamates that inhibit acetylcholinesterase in the mammalian brain after systemic administration. *Id*. at 4:16–20. Preferred compounds of the invention include N-ethyl, N-methyl-3[(1-dimethyl-amino)ethyl]phenyl carbamate, i.e., RA_7. *Id*. at 5:40–45, 12:56–60, 14:17–19. The compounds may be combined "with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice." *Id*. at 7:19–24. Rosin discloses administering the compounds of the invention, including RA_7, by "any conventional route." *Id*. at 13:8–10. Additionally, Rosin states:

> Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection. Buffers, preservatives, antioxidants and the like can be incorporated as required.
>
> Preferred antioxidants for use with the compounds of the present invention include sodium metabisulphite and ascorbic acid.

Id. at 7:45–50. Rosin discloses that compounds of the invention, including RA_7, showed greater in vivo potency than physostigmine, that "may be due" to factors including "greater chemical stability." *Id*. at 11:21–29.

3. Elmalem

Elmalem is a journal article discussing a study comparing the effects of three synthesized anticholinesterase agents, including RA_7, with those of physostigmine on the respiratory depression induced by morphine in rabbits.

Ex. 1009, 1059. Elmalem explains that physostigmine has "low chemical stability," whereas the three synthesized agents, including RA_7, have "a greater chemical stability." *Id*. Elmalem states that for the study all of these four drugs were "made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation." *Id*. at 1060.

4. Ebert

Ebert discloses a drug-containing adhesive composite transdermal delivery device comprising a substantially drug impermeable proximal release liner and a method for making the device. Ex. 1006, Abstract. Ebert explains that although its disclosure specifically refers to nicotine as the active drug, "any other liquid drug contained in an active gel which can be transdermally or transmucosally delivered may be substituted in place of nicotine." *Id*. at 15:30–35. With respect to nicotine, Ebert explains that a "trait of nicotine that can be problematic is its tendency to oxidize readily in the presence of light and air." *Id*. at 21:17–19. Ebert teaches that "[d]uring fabrication of nicotine patches, oxidation is controlled by addition of an antioxidant to the active gel," wherein BHT is a preferred antioxidant. *Id*. at 21:23–26. Ebert teaches mixing BHT with nicotine preferably in the range of about 0.01–1.0% w/w. *Id*. at 21:26–28.

5. Analysis

a. Claims 1 and 7

Petitioner asserts that Enz teaches a composition that meets every limitation of claims 1 and 7, except for the addition of an antioxidant, as previously discussed regarding the combination of Enz and Sasaki. Pet. 30, 38. Patent Owner does not dispute that Enz discloses those limitations of claims 1 and 7. *See* PO Resp. 21–22. Accordingly, our analysis turns to

whether the evidence establishes that, based on the combined teachings of Enz, the Handbook, Rosin, Elmalem, and Ebert, along with the knowledge generally available to one of ordinary skill in the art, it would have been obvious to a person of ordinary skill in the art at the time of the invention who endeavored to formulate rivastigmine into a transdermal patch, as taught by Enz, to have added an antioxidant.

As discussed previously, Petitioner asserts that at the time of the invention, a person of ordinary skill in the art who desired to formulate rivastigmine into a transdermal patch, as taught by Enz, would have investigated the stability of the drug. Pet. 32; Ex. 1010 ¶ 59. According to Petitioner and Dr. Kydonieus, each of Elmalem and Rosin informs such an investigation by teaching or suggesting the addition of an antioxidant to compositions comprising RA_7. Pet. 32 (citing Ex. 1009, 2; Ex. 1010 ¶ 59; Ex. 1008, 7:45–53). Petitioner asserts that a person of ordinary skill in the art would have understood from those references that RA_7 was susceptible to oxidation and "would have known that there would be little or no difference between rivastigmine and RA_7 with respect to oxidation." *Id*. at 32–33 (citing Ex. 1010 ¶ 60); *see also* Ex. 1010 ¶ 29 ("[A] teaching that the racemic compound RA_7 is susceptible to oxidative degradation is equally applicable to the single enantiomer rivastigmine.").

Further, Petitioner asserts that when investigating the stability of rivastigmine, a person of ordinary skill in the art "would have reasonably expected, based on the molecular structure of the drug, that rivastigmine would be susceptible to oxidative degradation." Pet. 34–35 (citing Ex. 1010 ¶ 63; Ex. 1011 ¶¶ 52–59). In particular, Petitioner submits the declaration of Dr. Schöneich as supporting the position that a person of ordinary skill in the

art would have recognized the similarities between the structure of rivastigmine and nicotine and "would have expected that rivastigmine would be susceptible to oxidative degradation at the benzylic C-H bond and adjacent tertiary amine via similar mechanisms as nicotine and to roughly the same extent as nicotine." *Id*. at 35–36 (citing Ex. 1011 ¶ 59).

In this vein, Petitioner asserts that "Ebert taught that nicotine was known to readily oxidize in the presence of light and air, and that adding an antioxidant . . . could reduce that oxidation." Pet. 36 (citing Ex. 1006, [21]). Therefore, according to Petitioner, a person of ordinary skill in the art would have had reason to combine rivastigmine with an antioxidant to protect against degradation with a reasonable expectation of successfully doing so based upon the knowledge of an ordinarily skilled artisan regarding the molecular structure of rivastigmine and the teachings of Rosin, Elmalem, and Ebert. *Id*. at 37 (citing Ex. 1006, 21; Ex. 1010 ¶¶ 63, 64; Ex. 1011 ¶ 61).

Patent Owner does not challenge as untrue Petitioner's assertion that a person of ordinary skill in the art who desired to formulate the transdermal patch disclosed by Enz into a commercially available product would have investigated the stability of the drug and formulation. *See, e.g.*, PO Resp. 9 (Patent Owner asserting only that Petitioner's "contention is not proof of obviousness"). Nor does Patent Owner challenge Petitioner's assertion that RA_7 and rivastigmine have similar stability. PO Resp. 14 n.2 (citing Ex. 2012 ¶ 96 n.8) (explaining that a person of ordinary skill in the art would have understood RA_7 and rivastigmine to have the same oxidative stability). Rather, Patent Owner asserts that, contrary to Petitioner's argument, the prior art does not teach or suggest that rivastigmine undergoes oxidative degradation or requires an antioxidant. PO Resp. 2.

In particular, Patent Owner asserts that Rosin does not teach or suggest any oxidative degradation problem for RA_7 or rivastigmine, and therefore, a skilled artisan would not have known or had any motivation to add an antioxidant to a rivastigmine formulation. *Id*. at 26–27. Relying upon the declaration of Dr. Klibanov, Patent Owner asserts that what a person of ordinary skill in the art would understand instead from Rosin is that RA_7 and rivastigmine are both oxidatively stable. *Id*. at 14–15, 26 (citing Ex. 2012 ¶¶ 48, 66; Ex. 1008, 3:37–39, 11:21–29). Patent Owner and Dr. Klibanov draw this conclusion from Rosin's teaching that compounds such as RA_7 show "greater chemical stability" than physostigmine. *Id*. However, as Dr. Klibanov has acknowledged, "Rosin does not mention the oxidative stability of RA_7 and contains no test data concerning such stability." Ex. 2012 ¶ 47. Absent any discussion by Rosin regarding the oxidative stability of the compound, Dr. Klibanov has not explained adequately why a person of ordinary skill in the art would infer from Rosin's disclosure that RA_7 and rivastigmine are both, in fact, oxidatively stable. Rosin describes physostigmine as "chemically unstable" with a short half-life of 20–40 minutes, and that it "must be prepared in solution with an antioxidant." Ex. 1008, 1:33–37. Thus, a comparative statement describing RA_7 as showing "greater chemical stability than physostigmine"[11] may indicate only that RA_7 is less "chemically unstable" than physostigmine. In this respect, we are ultimately persuaded that the evidence supports the

[11] We note that Rosin does not expressly teach that RA_7 shows greater stability than physostigmine. Rather, Rosin describes "a need to provide new carbamate derivatives which show greater stability than physostigmine," and suggests that the greater in vivo activity of RA_7 "may be due to" a number of factors, including, "greater chemical stability." Ex. 1008, 3:37–39, 11:23–29.

testimony of Dr. Kydonieus who explains that, to a person of ordinary skill in the art, Rosin's comparative statement "at best means that RA_7 is more stable than an unstable compound." Reply Decl. of Dr. Kydonieus, Ex. 1031 ¶ 48.

Further, Patent Owner asserts that Rosin does not teach or suggest any oxidative degradation problem for RA_7 or rivastigmine because Rosin's teaching to add an antioxidant "as required" is limited to injectable formulations. PO Resp. 27. According to Patent Owner, Petitioner's declarants, Dr. Kydonieus and Dr. Schöneich, agree that whether a drug oxidatively degrades is formulation specific. *Id*. (citing Ex. 1025, 95:24–96:18, 232:6–13, 258:8–13, 283:14–284:19; Ex. 1029, 53:10–17). Thus, Patent Owner asserts that even if a skilled artisan understood Rosin to suggest that an antioxidant may be required in an injectable formulation of RA_7, there would have been no reason to apply that teaching to the transdermal formulation of rivastigmine taught by Enz. *Id*. at 27–28 (citing Ex. 2012 ¶¶ 16, 50, 71).

Based on our analysis of the evidence, Dr. Kydonieus and Dr. Schöneich agree that the *susceptibility* of a compound to oxidatively degrade is not formulation specific. According to Dr. Kydonieus, a person of ordinary skill in the art "would not have understood the susceptibility of rivastigmine to oxidative degradation to vary based on method of drug delivery— the drug is inherently susceptible to oxidation, and this does not change based on the particular formulation, or the particular drug delivery method, in which the drug is employed." Ex. 1031 ¶ 54. With respect to Rosin, we note that apart from teaching the addition of an antioxidant "as required," Rosin discloses preferred antioxidants "for use with the

compounds of the present invention," without any indication that such use is limited to any particular formulation. Ex. 1008, 7:51–53. Indeed, Rosin discloses administering the compounds of the invention, including RA_7, by "any conventional route." *Id*. at 13:8–10. As Dr. Kydonieus explained persuasively, a person of skill in the art would have understood that transdermal administration was such a conventional route of administration. Ex. 1031 ¶ 53.

Although we do not agree with Patent Owner that Rosin teaches or suggests that rivastigmine is oxidatively stable, we also do not find that Rosin's disclosure, alone, would have suggested to a person of ordinary skill in the art that rivastigmine required an antioxidant. So, we continue our obviousness analysis by considering the additional prior art relied upon by the Petitioner and the evidence of knowledge in the art at the time of the invention.

Patent Owner asserts that Elmalem also does not teach or suggest that rivastigmine requires an antioxidant in any pharmaceutical formulation. PO Resp. 28 (citing Ex. 2012 ¶¶ 74, 108). As asserted with Rosin, Patent Owner contends that a person of ordinary skill in the art would have understood from Elmalem that RA_7 and rivastigmine are both oxidatively stable because Elmalem teaches that RA_7 has a "greater chemical stability" than physostigmine. *Id*. at 28–29 (citing Ex. 2012 ¶ 48). We remain unpersuaded by this argument for the same reasons discussed with respect to Rosin.

Additionally, Patent Owner asserts that Elmalem's statement that "[a]ll drugs were made up freshly in sterile saline, which included an equal weight of sodium metabisulphite, to prevent oxidation," did not mean that

the sodium metabisulphite, an antioxidant, was included to prevent oxidation of RA_7. PO Resp. 30–34. According to Patent Owner, the antioxidant was added instead only to prevent oxidation of one of the drugs, physostigmine, and was included in the preparation of the other drugs only as a control. *Id*. (citing Ex. 2012 ¶¶ 77–110).

We have considered Patent Owner's arguments in support of that contention, *see* PO Resp. 31–34, as well as the cited testimony of Dr. Klibanov, but do not find them to persuasively alter a plain reading of Elmalem's statement for the reasons discussed by Petitioner and Dr. Kydonieus. Pet. Reply 13; Ex. 1031 ¶¶ 56–63. In particular, we are not persuaded by Patent Owner's assertion that a person of ordinary skill in the art would have understood that Elmalem added antioxidant also to the saline-treated controls. PO Resp. 34. According to Patent Owner and Dr. Klibanov, Elmalem refers to the saline control preparation expressly as a "drug" in the "Summary" section, thus leading a skilled artisan to have understood that Elmalem included an antioxidant in the saline control preparation also. *Id*. at 32–33 (citing Ex. 2012 ¶ 104; Ex. 1009, 1059–60).

We disagree with Patent Owner. In the "Summary," or abstract, of Elmalem, it states, "Each drug, RA_6, (1 mg i.v., 2 mg s.c.) RA_7 (1 or 2 mg i.v.); RA_{15} (0.25 or 0.5 mg i.v.), physostigmine (0.05 or 0.1 mg i.v.) or saline (1 ml), was injected . . . ." Ex. 1009, 1059. We find that a person of ordinary skill in the art would have understood the saline to be separated from the "drug" listing, i.e., RA_6, RA_7, RA_{15}, and physostigmine, by the use of the term "or." That reading recognizing only 4 drugs is further supported by the statement in Elmalem's "Discussion" section that "[a] highly significant correlation was found for all 4 drugs . . . ." *Id*. at 1064.

Moreover, we note that Elmalem described expressly the critical aspects of its study, including the methods, materials, and controls, e.g., the "saline-treated controls." Ex. 1009, 1060. Rather than describing the addition of an antioxidant as a control, Elmalem specifically explained that the inclusion of the antioxidant in the preparation of each drug sample was "to prevent oxidation." *Id*.

Upon consideration of the evidence and arguments, we find no persuasive reason why a person of ordinary skill in the art would not understand Elmalem's disclosure of including an antioxidant in each drug sample, including the RA_7 sample, "to prevent oxidation" to mean anything other than just that.

Patent Owner asserts further that even if Elmalem is understood to suggest adding an antioxidant to an RA_7 or rivastigmine formulation, that teaching is limited to aqueous injectable formulations, and a person of ordinary skill in the art would not have been motivated to apply that suggestion to the transdermal rivastigmine formulation taught by Enz. PO Resp. 36 (citing Ex. 2012 ¶¶ 16, 50, 109). We remain unpersuaded by this argument for the same reason discussed with respect to Rosin, i.e., we find more persuasive the testimony of Dr. Kydonieus that a person of ordinary skill in the art would not have understood a susceptibility of rivastigmine to oxidative degradation to vary based on method of drug delivery, as the evidence suggests that the *susceptibility* to oxidation is a property of a compound that does not change based on the particular drug delivery method. Ex. 1031 ¶ 54.

Patent Owner asserts that neither the Handbook nor Ebert teach or suggest any oxidative problem for rivastigmine, or any other problem or

solution relevant to the manufacture of a rivastigmine transdermal device. PO Resp. 23–24, 37–40. However, Patent Owner does not address the usefulness of the Handbook for determining the optimal antioxidant and its concentration, or the relevance of Ebert's disclosure of a peelable impermeable backing material adapted for removal prior to administering the transdermal device, i.e., the releasable liner, as relied upon and established persuasively by the Petitioner. *Id*.

Turning to the knowledge in the art, Patent Owner asserts that contrary to Petitioner's argument, Pet. 34–36, a person of ordinary skill in the art would not have predicted that rivastigmine would oxidatively degrade based on its structure. PO Resp. 2, 16–20. In particular, Patent Owner challenges Dr. Schöneich's opinion that a person of ordinary skill in the art would have recognized rivastigmine as being susceptible to oxidative degradation based on the presence of two functional groups, i.e., a benzylic C-H bond and an adjacent tertiary amine. PO Resp. 17.[12] According to Dr. Schöneich, a person of skill in the art would have recognized also that rivastigmine and nicotine, a drug known to be susceptible to oxidative degradation at the time of the invention, as evidenced by Ebert, shared those structural similarities. Ex. 1011 ¶ 56. Patent Owner asserts that Dr. Schöneich's opinion is unsupported by a comparison of rivastigmine to

[12] Patent Owner challenges also Dr. Schöneich's discussion of dextromethorphan. PO Resp. 17. However, Petitioner has not relied on that discussion in the Petition or Reply Brief. Dr. Schöneich's discussion of dextromethorphan was exemplified only as a compound comprising one of the two functional groups forming the basis of his asserted susceptibility analysis. *See* Ex. 1011 ¶ 47; Ex. 1032 ¶ 64 (describing dextromethorphan as example of a drug having just one feature of the two features forming the basis of the asserted oxidative degradation susceptibility analysis for rivastigmine).

nicotine because nicotine does not have a benzylic C-H bond, but instead an N-substituted pyrrolidone. PO Resp. 17.

Although we agree with Patent Owner that nicotine does not have a benzylic C-H bond, Petitioner and Dr. Schöneich used the term "benzylic" in quotes, explaining specifically that with respect to the structure of nicotine, the term "'benzylic' is in quotes because the aromatic ring adjacent to the carbon identified with the arrow is a pyridine ring rather than a benzene ring." Ex. 1011 ¶ 49; *see also* Pet. 35, Fig. 1 (including quotes around the term "benzylic" when referring to the structure of nicotine). As Dr. Schöneich explained further, "the aromatic ring in nicotine contains a nitrogen and is therefore a pyridine aromatic ring, while the aromatic ring in rivastigmine has a carbon at that position and is called a benzene aromatic ring." Ex. 1032 ¶ 54. In other words, Dr. Schöneich's opinion did not rely upon or otherwise require nicotine to have a benzylic C-H bond. Rather, as Dr. Schöneich explained persuasively, a person of ordinary skill in the art would have understood that "the aromatic ring in both rivastigmine and nicotine would have the same effect on the adjacent carbon-hydrogen bond. Namely, both would cause that bond to be weaker by stabilizing a radical at that position by electron delocalization (also called resonance) in the aromatic ring." *Id*. (citing Ex. 1011 ¶¶ 27–31, 48–49). Patent Owner has not argued or established otherwise with persuasive evidence.

Patent Owner asserts also that Dr. Schöneich's opinion is unsupported by a comparison of rivastigmine to nicotine because no nicotine transdermal devices commercially available at the time of the invention were reported to include an antioxidant. PO Resp. 17–18 (citing Ex. 2012 ¶¶ 144–145, 150–151). Patent Owner acknowledges that nicotine was known at the time of

the invention to be susceptible to oxidative degradation; however, Patent Owner contends that because that knowledge did not motivate a person of ordinary skill in the art to add an antioxidant to nicotine, such knowledge of susceptibility to rivastigmine would not either. PO Resp. 18 (citing Ex. 2012 ¶¶ 150–151). As we have discussed previously, we find more credible the testimony of Dr. Kydonieus and Dr. Schöneich explaining that a person of ordinary skill in the art would have understood that a manufacturer could apply means to prevent oxidation in such commercial products other than by adding an antioxidant. *See, e.g.*, Ex. 1031 ¶ 90; Ex. 1032 ¶ 63.

After considering the record as a whole, and for the reasons discussed, we find that a person of ordinary skill in the art would have predicted that the transdermal formulation disclosed by Enz is susceptible to oxidative degradation and would have been motivated to add an antioxidant to the formulation with a reasonable expectation of successfully avoiding that predicted degradation. Accordingly, we conclude that the preponderance of the evidence demonstrates that the combined prior art renders obvious claims 1 and 7 of the '031 patent.

E. Obviousness of Claims 3 and 16 over Enz (Ex. 1002), the Handbook (Ex. 1003), Rosin (Ex. 1008) and Ebert (Ex. 1006)

Petitioner contends that claims 3 and 16 would have been obvious to a person of ordinary skill in the art at the time of the invention over the combination of Enz, the Handbook, Rosin, and Ebert. Pet. 41–43. Claim 3 depends from claim 1 and further recites "wherein the anti-oxidant is tocopherol, esters thereof, ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate." Claim 16 depends from claim 15 and further recites "wherein the anti-oxidant is tocopherol, esters thereof,

ascorbic acid, butylhydroxytoluene, butylhydroxyanisole or propyl gallate."

Petitioner asserts that a person of ordinary skill in the art would have been motivated to modify Enz's transdermal patch by adding an antioxidant for similar reasons discussed regarding the challenge of independent claims 1 and 15. Pet. 41–42. Additionally, Petitioner asserts that many of the antioxidants recited in claims 3 and 16 are listed in the Handbook. *Id*. at 42 (citing Ex. 1003, 3–23). According to Petitioner, a person of ordinary skill in the art at the time of the invention would have been motivated to select one of these known antioxidants listed in the Handbook because inclusion in the Handbook indicates approved use in pharmaceuticals. *Id*. (citing Ex. 1010 ¶ 74).

Further, Petitioner asserts that Rosin provides motivation with a reasonable expectation of success to select ascorbic acid as an antioxidant. *Id*. According to Petitioner, Rosin teaches that preferred antioxidants for use with compounds of its invention, e.g., RA_7, include ascorbic acid. *Id*. (citing Ex. 1008, 5:44–45, 7:51–53). Additionally, Petitioner asserts that Ebert provides motivation with a reasonable expectation of success to select BHT, BHA, and tocopherol by teaching the use of these antioxidants to prevent degradation of nicotine in transdermal devices. *Id*. (citing Ex. 1006, 21).

Patent Owner does not raise any separate argument regarding claims 3 and 16 or otherwise address this ground.

For similar reasons previously discussed, we are persuaded that Petitioner has established that the preponderance of the evidence shows that the combination of Enz, the Handbook, Rosin, and Ebert would have provided a reason to a person of ordinary skill in the art at the time of the invention to add an antioxidant to the composition disclosed by Enz.

Further, Petitioner has established persuasively that a person of ordinary skill in the art would have found it obvious to select one of the recited antioxidants in claims 3 and 16 that is listed in the Handbook, and/or specifically disclosed in Rosin or Ebert. Doing so would have amounted to combining a familiar element according to a known method to yield no more than a predictable result. *See KSR Int'l Co.*, 550 U.S. at 416.

Accordingly, we conclude that the preponderance of the evidence establishes that claims 3 and 16 would have been obvious over the combination of Enz, the Handbook, Rosin, and Ebert under 35 U.S.C. § 103(a).

IV. MOTION TO EXCLUDE

Petitioner moves to exclude Exhibits 2015, 2032, 2053, 2059 and 2061, along with paragraphs 27, 159 and 162–166 of Exhibit 2012, and sections 157:9–160:19, 171:16–179:10 and 185:24–189:6 of Exhibit 1049.[13] Paper 47, 1.[14] Additionally, Petitioner moves to exclude portions of the Patent Owner's Response, Dr. Klibanov's declaration, Ex. 2012, and the Deposition Transcript of Dr. Kydonieus, Ex. 1049, discussing the '031 Specification statement that "[i]t has now been found after exhaustive testing that compound A is susceptible to degradation, particularly in the presence of oxygen," Ex. 1001, 1:22–24. Paper 47, 1, 13–14. Patent Owner opposes

[13] Based on our review, Patent Owner has not referred to Exhibits 2059 and 2061, or sections 157:9–160:19, 171:16–179:10 and 185:24–189:6 of Exhibit 1049 in the Patent Owner Response.

[14] Petitioner asserts also that, to the extent that Patent Owner relies on Ex. 2059 or Dr. Schöneich's testimony regarding that exhibit in their Observations to Dr. Schöneich's April 18, 2015 deposition, such Observations should be "entitled to no weight." Paper 48, 1. We do not further address this assertion as it goes beyond addressing admissibility.

the motion. Paper 49. Petitioner responds to the opposition in a Reply in Support of the Motion to Exclude. Paper 57.

Because our Decision does not rely on the challenged content of Exhibits 2015, 2032, 2053, 2059, 2061, paragraphs 27, 159, and 162–166 of Exhibit 2012, or sections 157:9–160:19, 171:16–179:10 and 185:24–189:6 of Exhibit 1049, we dismiss Petitioner's Motion to Exclude those items as moot.

Moreover, to the extent that Petitioner contends that portions of the Patent Owner's Response, Dr. Klibanov's declaration, Ex. 2012, and the Deposition Transcript of Dr. Kydonieus, Ex. 1049, improperly rely upon unsupported statements and data from the '031 patent Specification, Paper 47, 13–14, we are not persuaded. According to Petitioner, Patent Owner should have provided a declaration from a person with first-hand knowledge of the experiments discussed in the Specification, as required by 37 C.F.R. § 42.61(c). Paper 47, 14. However, contrary to Petitioner's assertion, we do not find that Patent Owner relied on the referenced statement in the Specification, i.e., "[i]t has now been found after exhaustive testing that compound A is susceptible to degradation, particularly in the presence of oxygen," Ex. 1001, 1:22–24, to prove a fact other than what the Specification describes. *See* 37 C.F.R. § 42.61(c) (specification of a patent is admissible as evidence only to prove what the specification describes); *see also* 77 Fed. Reg. 48,612, 48,624 (Aug. 14, 2012) (explaining that 7 C.F.R. § 42.61(c) addresses the "problem in which a party mistakenly relies on a specification to prove a fact other than what the specification says").

Accordingly, we deny Petitioner's Motion to Exclude portions of Patent Owner's Response, Exhibit 2012, and Exhibit 1049 describing what

the Specification states.

V. CONCLUSION

We conclude that Petitioner has demonstrated by a preponderance of the evidence that claims 1–3, 7, 15, 16 and 18 instituted for *inter partes* review are unpatentable under 35 U.S.C. § 103(a) as follows:

Reference(s)	Basis	Claims
Enz, the Handbook, Rosin, Elmalem, and Ebert	§ 103(a)	1, 2, 7, 15 and 18
Enz, the Handbook, Rosin, and Ebert	§ 103(a)	3 and 16
Enz and Sasaki	§ 103(a)	1–3, 7, 15, 16 and 18

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner's Motion to Exclude is dismissed as moot with respect to Exhibits 2015, 2032, 2053, 2059, 2061, paragraphs 27, 159 and 162–166 of Exhibit 2012, and sections 157:9–160:19, 171:16–179:10 and 185:24–189:6 of Exhibit 1049;

Further ORDERED that Petitioner's Motion to Exclude is denied with respect to portions of the Patent Owner's Response, Dr. Klibanov's declaration, Ex. 2012, and the Deposition Transcript of Dr. Kydonieus, Ex. 1049, asserted to rely improperly upon unsupported statements and data from the '031 patent Specification;

FURTHER ORDERED that claims 1–3, 7, 15, 16 and 18 have been shown by a preponderance of the evidence to be unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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