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Paper 77
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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.*

DECISION
Denying Patent Owner's Request for Rehearing
37 C.F.R. § 42.71

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

I. INTRODUCTION

Novartis AG and LTS Lohmann Therapie-Systeme AG (collectively, "Patent Owner") request reconsideration of the Final Decision entered on September 28, 2015, Paper 69 ("Final Decision" or "Final Dec."). Paper 71 ("Rehearing Request" or "Req. Reh'g").

In the Final Decision, we addressed the following grounds of unpatentability for challenged claims 1–3, 7, 15, 16 and 18 of U.S. Patent No. 6,335,031 B1 (Ex. 1001, "the '031 patent"):

References	Basis	'031 Patent Claims
Enz,[2] the Handbook,[3] Rosin,[4] Elmalem,[5] and Ebert[6]	§ 103(a)	1, 2, 7, 15 and 18
Enz, the Handbook, Rosin, and Ebert	§ 103(a)	3 and 16
Enz and Sasaki[7]	§ 103(a)	1–3, 7, 15, 16 and 18

Petitioner relied on two declarations of Dr. Agis Kydonieus, Ex. 1010; Ex. 1031, and two declarations of Dr. Christian Schöneich, Ex. 1011; Ex. 1032. Patent Owner relied on the declaration of Dr. Alexander M. Klibanov, Ex. 2012.

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

In the Final Decision, we held that Noven Pharmaceuticals, Inc. and Mylan Pharmaceuticals Inc. (collectively, Petitioner) had shown by a preponderance of the evidence that claims 1–3, 7, 15, 16 and 18 of U.S. Patent No. 6, 335,031 B1 (Ex. 1001, "the '031 patent") are unpatentable for obviousness under 35 U.S.C. § 103(a). Final Dec. 42.

II. ANALYSIS

"When rehearing a decision on petition, a panel will review the decision for an abuse of discretion." 37 C.F.R. § 42.71(c). "The burden of showing a decision should be modified lies with the party challenging the decision. The request must specifically identify all matters the party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply." 37 C.F.R. § 42.71(d). For the reasons discussed below, Petitioner's Rehearing Request is *denied*.

A. Federal Circuit Decision in Watson

Patent Owner asserts that we overlooked the Federal Circuit's decision in *Novartis Pharms. 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")* in two respects. Req. Reh'g 2–7, 9–13. First, according to Patent Owner, "the Board erred in overlooking the Federal Circuit's holding in *Watson* that Elmalem would not have taught a person of ordinary skill in the art that rivastigmine is oxidatively unstable or required an antioxidant." *Id*. at 7.[8] Second, Patent Owner asserts that the Board overlooked the

[8] Patent Owner asserts also that we "overlooked that district court expert credibility determinations should be accorded great deference 'because the court saw the witnesses and heard the testimony.'" Req. Reh'g 6 (quoting *Celsis In Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 929 (Fed. Cir. 2012)).

Federal Circuit's holding in *Watson* that "'susceptibility' to oxidative degradation would not have motivated a person of ordinary skill in the art to add an antioxidant to the transdermal formulation in Enz." *Id*. at 9–10.

We have carefully reviewed Patent Owner's arguments presented in the Request for Rehearing, but do not find them persuasive. In particular, the Decision squarely addresses the Federal Circuit's decision in *Watson* and explains why that decision does not control in this proceeding. Final Dec. 4–5. Specifically, we stated:

> 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, 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, as required in district court litigation. 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.

Id.

Significantly, the Federal Circuit noted that "[t]he district court admitted that there 'does not appear to be an objectively 'correct' reading [of Elmalem]," rather both arguments regarding whether Elmalem teaches or suggests adding an antioxidant to rivastigmine "seem logical and are supported by highly qualified experts in the field." *Watson* at 992 (quoting *Novartis Pharm. Corp. v. Par Pharm., Inc.*, 48 F. Supp. 3d 733, 757 (D. Del. 2014). Further, the Federal Circuit explained that the district court credited

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However, the deference a district court receives for expert credibility determinations is accorded by the Federal Circuit reviewing an appeal from the district court, not by the Board in an *inter partes* trial proceeding.

Novartis' expert testimony as being more credible than Watson's expert. *Id.* at 993. Based upon that credibility assessment, the district court found that Elmalem's use of an antioxidant was to reduce variability among samples tested, and not a teaching or suggestion that rivastigmine is susceptible to oxidative degradation so as to motivate one of skill in the art to combine an antioxidant with it. *Id.* (citing *Novartis Pharm. Corp. v. Par Pharm., Inc.*, 48 F. Supp. 3d 733 at 756–57).

While acknowledging that "the plain language of the Elmalem article appears to present a close[] question," on appeal, the Federal Circuit gave "great deference" to the credibility determination of the district court. *Id.* at 996. Based upon that deference, the Federal Circuit affirmed the district court's holding that Watson failed to prove by clear and convincing evidence that the asserted claims of the '031 patent would have been obvious. *Id.* at 997.

In this proceeding, the Petitioners Noven and Mylan presented different evidence than what Watson presented in district court regarding what Elmalem would have taught a person of ordinary skill in the art. Specifically, the Petitioners relied upon the declaration testimony of Dr. Kydonieus and Dr. Schöneich. Patent Owner has not shown that the same declaratory evidence was presented in the district court case reviewed by the Federal Circuit. In the Decision, we explain our finding that Elmalem's disclosure suggests adding an antioxidant to rivastigmine to prevent oxidation was based upon our consideration of the evidence and arguments presented to us. Final Dec. 32. In particular, upon considering and comparing the testimony of Patent Owner's expert, Dr. Klibanov, with that

of Petitioner's experts, Drs. Kydonieus and Schöneich, we afforded greater persuasive weight to the testimony of Petitioner's experts. *See id*. at 31–35.

Thus, to the extent that Patent Owner asserts that the Board overlooked its burden under *In re Baxter International, Inc.*, 678 F.3d 1357, 1365 (Fed. Cir. 2012)("*Baxter*") to not arrive at a different conclusion than the Federal Circuit, Req. Reh'g 1, the argument is misplaced as the evidence and arguments presented in this proceeding differed from that considered by the court system in that litigation. *See Baxter* at 1365–66 (acknowledging burden of proof and record evidence considered by the Board was different than in court system and *affirming* the Board's different result, i.e., that the challenged claims were not patentable). As in *Baxter*, our expert credibility determination is not comparable to that of the district court, as we only considered the persuasive testimony of two experts "that had not been raised in the prior district court proceeding." *id.* at 1365. Thus, the Federal Circuit's deference to and affirmance of the credibility determinations of the district court do not control the outcome in this proceeding.

Regarding Patent Owner's assertion that, in Watson, the Federal Circuit "held that 'susceptibility' to oxidative degradation would not have motivated a person of ordinary skill in the art to add an antioxidant to the transdermal formulation in Enz," Req. Reh'g 9–10, we disagree with that characterization. To the contrary, the Federal Circuit stated, "here Watson *failed to prove* that a rivastigmine formulation was known to be susceptible to oxidative degradation." *Watson* at 996 (emphasis added). Additionally, the Federal Circuit explained that it gave considerable deference to the district court's finding that the prior art did not teach or suggest that rivastigmine was known to be susceptible to oxidative degradation, and that

"without an appreciation for rivastigmine's susceptibility to oxidative degradation, one of skill in the art would not have been motivated … to add an antioxidant to a rivastigmine formulation." *Id*. at 997. Moreover, we are not persuaded by Patent Owner's argument that we overlooked the Federal Circuit's affirmance of the district court's finding that the evidence did not teach or suggest rivastigmine's susceptibility to oxidative degradation because, as discussed above, the courts did not consider the same declaratory evidence presented in this proceeding.

Further, to the extent that Patent Owner asserts that we overlooked the Federal Circuit decision in *Watson* regarding the ground based upon the combined teachings of Enz and Sasaki, Req. Reh'g 14–15, we remain unpersuaded as the district court case reviewed by the Federal Circuit decision in *Watson* did not consider the combination of Enz and Sasaki. *See* Final Dec. 4–5 (explaining, among other differences, that in this proceeding "Noven presented additional prior art that was not before the Court in Watson").

B. Chemical Stability of Rivastigmine

Patent Owner asserts that the Board overlooked Patent Owner's evidence "that the Elmalem authors did not believe or reasonably expect rivastigmine to be oxidatively unstable or require an antioxidant." Req. Reh'g 7. In the Patent Owner Response, Patent Owner asserted that a person of ordinary skill in the art reading Elmalem would not have reasonably expected that rivastigmine would oxidatively degrade under pharmaceutically relevant conditions or require an antioxidant in any pharmaceutical formulation because two journal articles, Enz 1991 and Weinstock 1994, describing rivastigmine as showing "greater chemical

stability" than physostigmine, did not describe adding an antioxidant to rivastigmine. PO Resp. 36 (citing Ex. 2026 and Ex. 2027). In the rehearing request, Patent Owner asserts that because Weinstock 1994 was written by two of the Elmalem authors and they did not add an antioxidant to rivastigmine, it is apparent that they did not believe or reasonably expect rivastigmine to be oxidatively unstable or require an antioxidant. Req. Reh'g 7–8.

As indicated in the Decision, we considered each of Patent Owner's arguments, including those asserting an interpretation of Elmalem based upon the alleged teachings of Enz 1991 and Weinstock 1994. *See* Final Dec. 26 (referring to Patent Owner's Response at pages including those addressing Enz 1991 and Weinstock 1994). To the extent we might not have explained specifically why Patent Owner's arguments based upon Enz 1991 and Weinstock 1994 are not persuasive, we do so here.

As we discussed with respect to Rosin and Elmalem, a description that a compound shows "greater chemical stability" than another compound, is not necessarily a teaching that either compound is oxidatively stable. *See* Fin. Dec. 31–32. Indeed, as with Rosin and Elmalem, Enz 1991and Weinstock 1994 do not address oxidative stability. Dr. Kydonieus' explanation regarding the "greater chemical stability" description in Rosin is applicable here also, i.e., that to a person of ordinary skill in the art, the comparative statement "at best means that RA_7 is more stable than an unstable compound." Fin. Dec. 32 (quoting Ex. 1031 ¶ 48).

Moreover, Dr. Kydonieus addressed Enz 1991 and Weinstock 1994, explaining how Patent Owner's declarant, Dr. Klibanov, mischaracterized those publications as suggesting that rivastigmine is oxidatively stable. Ex.

1031 ¶¶ 68–70. In particular, Dr. Kydonieus noted that Enz 1991 described rivastigmine by stating the "drug appears to have greater chemical stability and longer duration of action than does physostigmine" based upon administration to human volunteers, suggesting that Enz 1991 is referring to the duration of action of rivastigmine in the body. *Id*. at 68–69 (quoting Ex. 2026, 272). Similarly, Dr. Kydonieus noted that Weinstock 1994 states, "In animals and human subjects [rivastigmine] showed superior chemical stability, oral bioavailability and a longer duration of action than physostigmine," suggesting that Weinstock 1994 is referring to in vivo activity of rivastigmine rather than oxidative stability in a pharmaceutical formulation. *Id*. at 70 (quoting Ex. 2027, 219).

Therefore, for reasons similar to those provided in the Final Decision regarding the relative chemical stability of rivastigmine disclosed by Rosin and Elmalem, we were not persuaded by Patent Owner's arguments regarding similar statements in Enz 1991 and Weinstock 1994. Thus, Patent Owner has not established that we overlooked its argument.

C. Other Compounds Not Reported To Include an Antioxidant

Patent Owner asserts that "the Board overlooked Patent Owner's evidence of multiple compounds with the same structural features as rivastigmine that were not reported in the prior art to be oxidatively unstable or to contain an antioxidant in their commercial formulations." Req. Reh'g 8 (citing PO Resp. 18; Ex 2012 ¶¶ 133–137). According to Patent Owner, we neither mentioned those exemplary compounds in our Final Decision, nor offered any reason why a person of ordinary skill in the art would ignore them. *Id*.

We disagree. As indicated in the Final Decision, we considered Patent Owner's argument. *See* Final Dec. 12 (referring to Patent Owner's Response at pages including those addressing exemplary compounds sharing structural features with rivastigmine). To begin, we note that Patent Owner did not mention by name any of the "multiple exemplary compounds" in the Patent Owner's Response. *See* PO Resp. 18 (referring to examples of compounds having features similar to rivastigmine, without identifying those examples). Instead, Patent Owner referred to the sections of Dr. Klibanov's declaration that address those examples. *Id*. (citing Ex. 2012 ¶¶ 133–137). Patent Owner relies on those same sections of Dr. Klibanov's declaration elsewhere in the Patent Owner's Response also. *See., e.g.*, PO Resp. 42.

In the Final Decision, we address specifically each of the examples Dr. Kydonieus described in those sections of his declaration. *See* Final Dec. 19–20. Significantly, we explained that merely identifying examples of drugs having structural similarities to rivastigmine that were "not reported to contain antioxidants in their commercial transdermal formulations," Ex. 2012 ¶ 133, was insufficient to establish that the compounds were not susceptible to oxidative degradation in pharmaceutically relevant conditions. Final Dec. 20–21. We explained further that neither Patent Owner nor Dr. Klibanov identified any statement in the Physician's Desk Reference upon which Dr. Klibanov relied in support of his assertions, or elsewhere, describing the oxidative stability or shelf-life of any of the asserted exemplary compounds. *Id*. at 19–20.

We also explained that it was problematic that Dr. Klibanov did not discuss in his declaration whether the commercial formulations comprising those exemplary compounds addressed drug stability by some means other

than adding an antioxidant. *Id*. at 20. As we stated in the Final Decision,

> 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.

Final Dec. 20. Thus, Patent Owner has not established that we overlooked its argument.

D. The European Agency Guidelines

Patent Owner asserts that we overlooked its evidence that a person of ordinary skill in the art would not add an antioxidant unless one was needed. Req. Reh'g 13. In particular, Patent Owner refers to a publication by The European Agency for the Evaluation of Medicinal Products providing guidance on the inclusion of antioxidants and antimicrobial preservatives in medicinal products ("EMEA guidelines"). *Id*. (citing Ex. 2019, 3).

As indicated in the Final Decision, we considered this argument by Patent Owner. *See* Final Dec. 12 (referring to Patent Owner's Response at pages including those addressing the EMEA guidelines). To the extent we might not have explained specifically why the argument was unpersuasive, we do so here. In the Patent Owner Response, Patent Owner asserted that the art expressly taught that antioxidants "should only be used once it has been shown that their use cannot be avoided." PO Resp. 10. In support of that contention, Patent Owner relied on the declaration of Dr. Klibanov and the EMEA guidelines. *Id*. at 9-10. According to Dr. Klibanov, the EMEA is the European equivalent of the United States Food and Drug Administration. Ex. 2012 ¶ 40. Dr. Klibanov did not provide testimony that the EMEA

"guidelines" represent anything more than just that. In other words, Patent Owner did not establish that the EMEA guidelines represented a restriction, rule or regulation for drug formulation in Europe, or that an approach that differed from those set forth in the guidance would not be approved by the agency, if, in fact, the agency is responsible for approving drugs.

Moreover, as Dr. Kydonieus explained, the EMEA guidelines are directed toward justifying the use of an antioxidant. Ex. 1031 ¶ 93. The EMEA guideline states, "Antioxidants should not be used to disguise poorly formulated products or inadequate packaging. The need to include an antioxidant should be explained and fully justified." Ex. 2019, 2. Thus, we understand the guidance as a whole to be directed to avoiding the use of an antioxidant to cure inadequate formulation or packaging techniques, rather than categorically avoiding the addition of an antioxidant to prevent oxidative degradation in compounds with known susceptibility to such degradation.

As discussed in the Final Decision, based on our consideration of the record as a whole, we found that Petitioner established that a person of ordinary skill in the art would have predicted that the transdermal formulation disclosed by Enz was susceptible to oxidative degradation and would have been motivated to add an antioxidant with a reasonable expectation of successfully avoiding that predicted degradation. *See, e.g.*, 17 (addressing the combination of Enz and Sasaki) and 38 (addressing the combination of Enz, the Handbook, Rosin, Elmalem, and Ebert).

Thus, Patent Owner has not established that we overlooked its argument or evidence.

III. CONCLUSION

We have considered Patent Owner's request, but find no point of law or fact which we overlooked or misapprehended in arriving at our Final Decision.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that the Patent Owner's request for rehearing is *denied*.

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