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On Behalf Of:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVEN PHARMACEUTICALS INC.
AND MYLAN PHARMACEUTICALS INC.,
Petitioners

v.

NOVARTIS AG AND LTS LOHMANN THERAPIE-SYSTEME AG,
Patent Owners

Inter Partes Review No. 2014-00549[1]

U.S. Patent 6,316,023

PATENT OWNERS' MOTION FOR OBSERVATIONS ON CROSS-EXAMINATION OF CHRISTIAN SCHÖNEICH, Ph.D.

[1] Case IPR2015-00265 has been joined with this proceeding.

I. A POSA Would Not Have Reasonably Predicted That Rivastigmine Undergoes Oxidative Degradation Under Pharmaceutically Relevant Conditions Based On Its Structure

At Ex. 1048, page 22, line 6 to page 23, line 22, Dr. Schöneich testified that the bond dissociation energy "does not tell you under which conditions you form radicals in any chemical reaction."[2] This testimony is relevant to Dr. Schöneich's assertion that a bond's strength was not a theoretical issue in ¶ 8 of Ex. 1032. This testimony is relevant because it demonstrates that a POSA would not have reasonably predicted that rivastigmine would undergo oxidative degradation under pharmaceutically relevant conditions based on its structure.

At Ex. 1048, page 21, line 9 to page 22, line 5, Dr. Schöneich admitted that Carey and Sundberg (Ex. 1018 at 693) provides only "relative reactivities, not absolute reactivities" of aromatic hydrocarbons. (*See also* Ex. 1032 at ¶ 9.) The testimony is relevant to Dr. Schöneich's assertion that a POSA would have predicted that rivastigmine is "susceptible" to oxidative degradation based on its structure in ¶ 14 of Ex. 1032. This testimony is relevant because it demonstrates that a POSA would not have reasonably predicted that rivastigmine would undergo oxidative degradation under pharmaceutically relevant conditions based on its structure.

[2] At Ex. 1048, page 7, line 25 to page 8, line 3, Dr. Schöneich agreed that answers he gave during cross-examination applied in both IPR proceedings.

At Ex. 1048, page 75, line 9 to page 76, line 7, Dr. Schöneich admitted that, other than protonation, the structure of the drug is the same irrespective of the dosage form. This testimony is relevant to Dr. Schöneich's assertion that a POSA would have predicted that rivastigmine is "susceptible" to oxidative degradation based on its structure in ¶ 15 of Ex. 1032. This testimony is relevant because Dr. Schöneich further admitted that, although the structure of the drug is the same, the dosage form can determine whether or not an antioxidant is required. (Ex. 1048 at 70:21-71:12.) Thus a POSA would not have reasonably predicted from its structure that rivastigmine would undergo oxidative degradation under pharmaceutically relevant conditions or require an antioxidant.

At Ex. 1048, page 16, lines 6 to 16 and page 108, lines 6 to 19, Dr. Schöneich admitted that there is no prior art literature that sets out the mechanism or site of oxidative degradation of rivastigmine and that he did not know what products are formed by its oxidative degradation. This testimony is relevant to Dr. Schöneich's assertion that a POSA would have predicted that rivastigmine is "susceptible" to oxidative degradation based on its benzylic carbon-hydrogen bond and adjacent tertiary amine in ¶ 14 of Ex. 1032. This testimony is relevant because it shows that Dr. Schöneich's structural theory is unproven.

At Ex. 1048, page 96, line 2 to 5, Dr. Schöneich testified that dextromethorphan is "susceptible" to oxidative degradation at the benzylic

position. This testimony is relevant to Dr. Schöneich's assertion that the benzylic position is "especially susceptible to oxidation" in ¶ 11 of Ex. 1032. This testimony is relevant because, even though dextromethorphan has a benzylic carbon, it was reported in the art to be "very stable," "[s]table under all normal conditions of storage," and to show "[e]xcellent stability" under pharmaceutically relevant conditions. (Ex. 2012 at ¶¶ 139-143.) Thus theoretical "susceptibility" to oxidative degradation does not correlate with the pharmaceutical reality of whether a compound undergoes oxidative degradation under pharmaceutically relevant conditions or requires an antioxidant.

At Ex. 1048, page 100, lines 7 to 19 and page 101, line 21 to page 102, line 8, Dr. Schöneich admitted that Boccardi 1994 reports that the 10-keto degradant of dextromethophan was found only in "trace amounts" during preformulation (a fact he omitted from his Reply Declaration) and that Boccardi 1994 does not report the conditions under which those trace amounts formed. (*See also* Ex. 2050 at 433.) This testimony is relevant to Dr. Schöneich's opinion that Boccardi 1994 teaches a POSA that dextromethorphan is "susceptible" to oxidative degradation without the accelerated conditions described in Boccardi 1989 in ¶ 62 of Ex. 1032. This testimony is relevant because it contradicts that opinion and demonstrates that Dr. Schöneich mischaracterized the teaching of Boccardi 1994.

At Ex. 1048, page 96, line 18 to page 17, line 14, Dr. Schöneich admitted

that Boccardi 1989 states that "the irradiation of an aqueous or acidic solution of [dextromethorphan hydrobromide] in the absence of Fe(III) ions did not induce any decomposition, irrespective of the presence or absence of molecular oxygen." (*See also* Ex. 1020 at 308.) This testimony is relevant to Dr. Schöneich's opinion that Boccardi 1989 teaches a POSA that dextromethorphan is "susceptible" to oxidative degradation without the accelerated conditions described in that article in ¶ 62 of Ex. 1032. This testimony is relevant because it shows that Boccardi 1989 reports that dextromethorphan does not oxidize in the absence of Fe(III) ions and that Dr. Schöneich mischaracterized the teaching of Boccardi 1989.

At Ex. 1048, page 100, line 20 to page 102, line 8 and page 113, line 13 to page, 114, line 14, Dr. Schöneich alleged that the Boccardi 1989 and 1994 references teach that dextromethorphan had stability problems and that a POSA would have been concerned by trace amounts of degradation during preformulation because Boccardi 1994 does not disclose the conditions under which the degradant formed. This testimony is relevant to those opinions. This testimony is relevant because it is contradicted by the express teaching in the art that dextromethorphan is "very stable" under pharmaceutically relevant conditions. (Ex. 2012 at ¶¶ 139-143.)

At Ex. 1048, page 48, lines 16 to 23, Dr. Schöneich admitted that he did not cite any literature indicating that any of the multiple real-world pharmaceutical

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