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 IPR2014-00549[1]

U.S. Patent No. 6,316,023

PETITIONERS' RESPONSE TO PATENT OWNERS' MOTION FOR OBSERVATIONS ON CROSS-EXAMINATION OF DR. SCHÖNEICH

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

Response to p. 1 ¶ 1: The testimony cited by Patent Owners demonstrates neither that bond strength is theoretical nor "that a POSA would not have reasonably predicted that rivastigmine would undergo oxidative degradation" based on its structure as Patent Owners assert. (Paper 45 at 1.) Dr. Schöneich testified that the bond dissociation energies reported in Carey & Sundberg ("C&S") (Ex. 1018) are "absolute values" and are "independent of the measurement." (Ex. 1048 at 23:8-14, discussing ¶13 of Dr. Schöneich's Reply Declaration (Ex. 1032), which reproduces bond dissociation energy values from C&S (Ex. 1018 at 683).) As Dr. Schöneich testified, the bond dissociation energy (i.e., bond strength) for a particular bond in a molecule is an inherent property of the molecule based on its chemical structure. (Ex. 1026 at 58:13-21.) Because rivastigmine has three structural features immediately adjacent to a particular carbon-hydrogen ("C-H") bond, a POSA would have immediately identified this bond as especially weak and particularly susceptible to oxidation. (Ex. 1011 ¶¶ 12, 55; Ex. 1026 at 48:2-49:13, 73:17-76:22; Ex. 1032 ¶¶ 14-15.)

Response to p. 1 ¶ 2: The testimony cited by Patent Owners does not demonstrate "that a POSA would not have reasonably predicted that rivastigmine would undergo oxidative degradation" based on its structure as Patent Owners assert. (Paper 45 at 1.) Dr. Schöneich did not testify that C&S "provides ***only*** relative reactivities, not absolute reactivities of aromatic hydrocarbons" as Patent

Owners assert. (*Id.*, emphasis added.) It was Patent Owners' questioning that related ***only*** to a single table in C&S that shows the relative reactivities of aromatic hydrocarbons. These relative reactivities are important to demonstrate that a C-H bond at a benzylic position, that is also a tertiary position (as in rivastigmine), is 67 times more reactive to oxygen than a C-H bond in a benzylic position alone. (Ex. 1032 ¶ 13, citing Ex. 1018 at 693.) Patent Owners further mischaracterize Dr. Schöneich's testimony, because he also testified that C&S provides the absolute bond strengths of tertiary and benzylic C-H bonds in the table of bond dissociation energies and states that "Benzylic, allylic, and tertiary positions are especially susceptible to oxidation." (Ex. 1032 ¶¶ 8, 10, 11, citing Ex. 1018 at 683, 693.) This testimony demonstrates that a POSA would have reasonably predicted that rivastigmine would undergo oxidative degradation based on its chemical structure because the POSA would have recognized that a particular C-H bond in rivastigmine is especially weak and therefore susceptible to oxidation.

Response to p. 2 ¶ 1: The testimony cited by Patent Owners does not demonstrate that "a POSA would not have reasonably predicted from its structure that rivastigmine would undergo oxidative degradation . . . or require an antioxidant" as Patent Owners assert. (Paper 45 at 2.) Dr. Schöneich testified that a POSA would understand that "oxidation reactions usually occur significantly slower" in the dry state. (Ex. 1048 at 70:7-20, *see also* Ex. 1032 ¶ 48) Thus, a

POSA would have understood that an antioxidant may not be necessary even for an oxidation-sensitive drug when is it formulated as a dry dosage form. (Ex. 1048 at 69:18-70:2, quoting Ex. 1032 ¶ 48.)

Response to p. 2 ¶ 2, p. 5 ¶ 1, p. 12 ¶ 1: Patent Owners' assertions that Dr. Schöneich's "structural theory is unproven" (Paper 45 at 2, 5-6) is not supported by the testimony cited by Patent Owners. Dr. Schöneich testified that a POSA would have immediately recognized that rivastigmine was particularly susceptible to oxidation due to the presence of ***three structural features***[2] immediately adjacent to a C-H bond that a POSA would understand to cause that bond to be especially weak and therefore readily oxidized. (Ex. 1026 at 48:2-49:13; Ex. 1011 ¶¶ 12, 53-55; Ex. 1032 ¶¶ 7-15) The support for Dr. Schöneich's opinion is drawn from a standard textbook, Carey & Sundberg (Ex. 1018), which identifies these same structural features as causing adjacent C-H bonds to be "especially weak" and therefore prone to oxidation. (Ex. 1032 ¶¶ 7-15; Ex. 1026 at 58:3-68:15.)

In addition, Dr. Schöneich provided nicotine as an example of a drug with

[2] Patent Owners mischaracterize Dr. Schöneich's' opinion by reciting only two of the three structural features identified by Dr. Schöneich that a POSA would have recognized as causing a particular C-H bond in rivastigmine to be especially weak and therefore particularly susceptible to oxidation. (Ex. 1011 ¶¶ 12, 55; Ex. 1026 at 48:2-49:13, 73:17-76:22; Ex. 1032 ¶¶ 14-15.)

the same three key structural features as rivastigmine that was known to undergo oxidation at the subject C-H bond and was known to oxidatively degrade in pharmaceutical formulations including transdermal patches. (Ex. 1026 at 84:17-89:20; Ex. 1027 at 452:1-5, 563:3-7; Ex. 1032 ¶¶ 46, 56-59.)

Response to p. 2 ¶ 3: Patent Owners' conclusion that "theoretical 'susceptibility' to oxidative degradation does not correlate with the pharmaceutical reality" (Paper 45 at 2-3) is not supported by the cited testimony. It was not merely an "assertion" of Dr. Schöneich's that the benzylic position is "especially susceptible to oxidation." Rather, Dr. Schöneich's testimony is supported by, and indeed quoted from, a standard chemistry textbook, Carey & Sundberg. (Ex. 1018 at 693.) Dextromethorphan was reported to be only "moderately stable" and had been observed to oxidatively degrade. (Ex. 1020 at 308; Ex. 1032 at 61.)

Response to p. 3 ¶ 1 and p. 4 ¶ 1: Patent Owners incorrectly assert that Dr. Schöneich mischaracterized the teachings of Boccardi 1994 (Ex. 2050) and Boccardi 1989 (Ex. 1020). As Dr. Schöneich testified, Boccardi 1989 states that dextromethorphan is only "moderately stable" and investigated the degradation of dextromethorphan they had previously observed and assumed was due to the presence of trace amounts of iron in glassware. (Ex. 1048 at 113:13-114:17; *see also* Ex. 1032 ¶ 61; Ex. 1020 at 308.) Boccardi 1994 states that the product of oxidative degradation (i.e., 10-ketodextromethorphan), was found in trace amounts

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