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 IPR2014-00550[1]

U.S. Patent No. 6,335,031

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

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

Response to Page 1, ¶ 1: Because a POSA would have known that physostigmine was unstable, Weinstock 1994 (Ex. 2027) only shows at most that rivastigmine was more stable than a very unstable compound. (Ex. 1049 at 97:17–98:4; Ex. 1031 at ¶¶ 48, 59 n.13.)

In any case, Patent Owners mischaracterize Dr. Kydonieus' testimony at (Ex. 1049 at 69:6–20), which does not refer to Weinstock 1994, but instead is immediately preceded and followed by questions regarding the Weinstock 1981 reference (Ex. 1049 at 68:10–69:5, 69:21–70:16). Dr. Kydonieus opined in his declaration that a POSA would have understood Weinstock 1994 to refer to rivastigmine as having greater *in vivo* activity than physostigmine "in humans and animals" (a phrase that Dr. Klibanov omitted when quoting the reference in his declaration), not to refer to oxidative stability of rivastigmine. (See Ex. 1031 at ¶ 70.)

Dr. Kydonieus testified that Elmalem (Ex. 1009) and Weinstock 1981 (Ex. 2046) are both publications of Professor Weinstock-Rosin's research group, and the use of very similar language in Weinstock 1981 to describe the addition of an antioxidant to certain drugs "to prevent oxidation" would not have been understood by a POSA to be a mere coincidence. (Ex. 1049 at 68:10–71:5.)

Dr. Kydonieus' testimony is relevant to, and consistent with, his opinion that the statement in Weinstock 1981(Ex. 2046) that an antioxidant was added to

compositions of morphine and physostigmine, both of which were known to be susceptible to oxidation, "to prevent oxidation" of these drugs, would have been considered by a POSA in interpreting the statement in Elmalem (Ex. 1009) that an antioxidant was added to drugs, including RA_7, "to prevent oxidation" of those drugs. (See Ex. 1049 at 68:10–70:18; Ex. 1031 at ¶¶ 59–60.)

Response to Page 1, ¶ 2: The statement from Enz 1991 to which Patent Owners addressed questioning does not inform the POSA of rivastigmine's absolute stability, because even if rivastigmine were understood to be more stable than physostigmine, as Dr. Kydonieus testified, that would at most mean it was *comparatively* more stable than a compound with "very bad chemical stability" that "has very short duration of action." (Ex. 1049 at 208:1–18.) Further, as Dr. Kydonieus opined, a POSA considering the statement from Enz 1991 as a whole would have understood it to refer to duration of action of rivastigmine in the body (*in vivo*). (Ex. 1031 at ¶ 69.)

Response to Page 2, ¶¶ 1–2 and Page 3, ¶ 1: That rivastigmine has greater claimed stability than physostigmine does not inform the POSA of the absolute stability of rivastigmine, as physostigmine is a very unstable compound that was known to be subject to both fast hydrolysis and oxidative degradation. (Ex. 1049 at 97:3:14, 17–98:4; Ex. 1031 at ¶¶ 48, 59 n.13; Ex. 2012 at ¶ 48.) Dr. Kydonieus testified that Rosin (Ex. 1008) states that physostigmine has a short half-life. (Ex.

1049 at 97:17–98:4.) He also testified that Rosin indicates that physostigmine is subject to oxidative degradation. (Ex. 1049 at 97:3–14.) Dr. Klibanov admitted that physostigmine is subject to hydrolysis. (Ex. 2012 at ¶ 48.) The testimony cited by Patent Owners is relevant to, and consistent with, Dr. Kydonieus' opinion that physostigmine was known by a POSA to be unstable, with a short 20-40 minute half-life, and with his opinion that Connors (Ex. 1015) lists physostigmine as a drug that was reported as susceptible to oxidative degradation. (Ex. 1031 at ¶¶ 48, 59 n.13.)

Response to Page 3, ¶ 2: The testimony cited by Patent Owners does not demonstrate a link between *in vivo* potency and oxidative stability, because Patent Owners confuse *in vivo* potency with the absolute concentration of drug in a composition. (See Ex. 1049 at 9:13–10:16.)

In any event, the cited testimony does not support Patent Owners' conclusion, as Dr. Kydonieus testified that Rosin (Ex. 1008) lists four different reasons that may account for greater *in vivo* potency of a drug, including higher lipid solubility and more-efficient gastrointestinal adsorption. (Ex. 1049 at 104:12–17; Ex. 1008 at 11:26–35.)

Response to Page 4, ¶¶ 1–2 and Page 6, ¶ 1: Patent Owners confuse the predictability of rivastigmine's oxidative degradation, which was apparent to a POSA based on its structure, with the testing that a formulator may have conducted

to confirm this expectation; Dr. Kydonieus has explained both points and how they relate. (See Ex. 1031 at ¶¶ 8–10.) Dr. Kydonieus testified that a POSA would have understood that rivastigmine was susceptible to oxidative degradation and would likely degrade in any particular formulation unless such degradation was protected against with an antioxidant. (Ex. 1049 at 128:16–129:15.)The formulator would then perform tests, as Dr. Kydonieus testified, to determine "the best amount of antioxidant you can use to get the best protection." (Ex. 1049 at 129:9-15.) He also testified that a POSA would not have been surprised to observe degradation of rivastigmine in a particular formulation. (Ex. 1049 at 150:23–151:21.) Dr. Kydonieus also testified that drug degradation is undesirable because it weakens drug potency, and also because the degradation byproducts could be toxic. (Ex. 1049 at 9:13–10:16.) This testimony is relevant to, and consistent with, Dr. Kydonieus' opinion that a POSA would have been motivated to add an antioxidant to a rivastigmine formulation to arrest its expected oxidative degradation. (See Ex. 1031 at ¶¶ 92–94.)

Response to Page 4, ¶ 3: Dr. Kydonieus testified that salts better resist oxidative degradation than bases. (Ex. 1049 at 93:18–94:5.) This testimony is relevant to, and consistent with, the opinion of Dr. Schoneich that the salt form of a drug is generally less susceptible to oxidation than the free base form, and in particular that oxidation is usually substantially reduced when the drug is

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