UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC, Plaintiffs,	:	Civil Action No. 12-2867-MLC-DEA
v.	:	District Judge Mary L. Cooper Magistrate Judge Douglas E. Arpert
DR. REDDY'S LABORATORIES, LTD. and DR. REDDY'S LABORATORIES, INC., Defendants.	: x	

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UNDER DISCOVERY CONFIDENTIALITY ORDER

EXPERT REPORT OF DR. JOANNE BROADHEAD

pharmaceutical formulations of palonosetron contain EDTA. ('980 Patent Exs.4, 5, 8; 3:14-20.) According to one of the Syntex formulators and named inventor, Mr. Malefyt, "EDTA was an important component" for stability of the palonosetron formulation. (ANDA Litigation Malefyt Tr. 65:9-14.) As Mr. Malefyt further explained, the EDTA formulation of palonosetron had the best stability, and a formulation sent to Japan that did not include EDTA required refrigeration and was unstable. (*Id.* 86:14-25.) The only formulations of which Mr. Malefyt was aware that improved on the stability of Phase II clinical trial formulations were formulations that contained EDTA. (*Id.* 87:4-10.)

47. Documents submitted on behalf of the Patent Owner also confirm that EDTA was represented to be important to stability of palonosetron formulations. For example, in a February 9, 2009 declaration, Danielle Bonadeo, a Helsinn employee and named inventor, made numerous statements that the presence of EDTA improves stability under certain circumstances. (Bonadeo Decl. ¶¶ 15-18, Feb. 9, 2009.) Likewise, a Teva witness at the ANDA trial testified that batches of Teva palonosetron formulations in which EDTA was removed did not meet stability parameters. (ANDA Litigation Zahavi Tr. 114:11 - 119:9.)

48. In fact, the patent owner recommended that formulations without EDTA used in Phase II studies, which included palonosetron at a low concentration (0.1 and 0.5 mg/ml), with a tonicifying agent (sodium chloride) and a phosphate buffer, be refrigerated. (*See* Summary of CMC at HELSN0334983 ("Phase I and II clinical studies were conducted with phosphate-buffered, pH 7.4 solutions of palonosetron. These formulations were not optimized for chemical stability, and refrigeration was required to achieve an adequate shelf-life for the clinical studies."); *id.* Table; Stability Statement at HELSN0128735 ("RS-25259 has been formulated as injectable solutions for clinical study containing either 0.10, 0.5, or 1.0 mg/ml of

free base in a sodium phosphate buffer at pH 7.4 with NaCl added to render the solutions isotonic. . . . [W]e recommend a 12 month shelf life for this product when stored at refrigerated conditions (5°±3°C).”).) When the Patent Owner changed those formulations for Phase III studies to include EDTA and citrate, refrigeration was not necessary. (Summary of CMC at HELSN0334983 (“The proposed Phase III/commercial formulations have been optimized for a longer shelf-life by decreasing palonosetron concentration, selecting the pH of maximum stability (5.0), employing citrate buffer and EDTA as chelating agents, and changing the tonicifying agent from sodium chloride to mannitol. Accelerated stability studies predict the room-temperature shelf-life of the improved formulations will be in excess of three years.”).)

49. Even where EDTA and citrate are included, as in Examples 4, 5, and 8 in the patent specification, there is no indication of what stability resulted from the addition of EDTA and citrate, or how stable the formulations of each of the examples were.

50. Furthermore, regulatory guidance states that antioxidants, including antioxidant synergists such as chelating agents, “should only be included in a formulation if it can be proved that their use cannot be avoided.” (European CPMP Guidance at Section 2; *see also* Swarbrick at 143.) The inclusion of EDTA in Examples 4, 5 and 8 of the patent implies that EDTA was necessary for stability. The patent does not explain how the claimed stability can be achieved without such a necessary component.

51. The inclusion of EDTA presented challenges in developing a globally acceptable formulation with regard to the uncertainty around the acceptability of an EDTA-containing formulation in Japan. (ANDA Litigation Malefyt Tr. 86:19-25.) The continued development and commercialization of an EDTA-containing formulation indicates that the Patent Owner believed the EDTA to be a necessary component in achieving the desired shelf life.

52. Many of the asserted claims do not require a chelating agent at all, but rather state that a chelating agent is "optional." (*See* '980 Patent cls.1-5, 16; '094 Patent cls.22-25.) These claims purport to cover a broad range of compositions including those that include some chelating agent and those that do not. For the asserted claims of the '980 and '094 Patent, which do not require EDTA, there is no enabling disclosure as to how to achieve the claimed levels of stability without undue experimentation. Claims 1 and 16 of the '980 Patent are particularly broad in that they do not require *any* of the formulation features (such as chelating agents, citrate buffers, mannitol, or pH adjustments) alleged to enhance stability, and there is no enabling disclosure that supports these broad claims. Even for claim 6 of the '980 Patent and claim 27 of the '094 Patent, which require an unspecified chelating agent, there is no disclosure of how to obtain the claimed stability without the specific chelating agent EDTA.

53. Moreover, the common specification teaches enhancing stability with EDTA only in formulations that also include a citrate buffer. (*See* '980 Patent 3:13-19.) All disclosed examples of pharmaceutical formulations of palonosetron contain citrate buffer. (*Id.* Exs.4, 5, 8.) Nevertheless the broad patent claims seek to include formulations which do not include a buffer ('980 Patent cls.1, 16) or which are buffered with an unspecified buffer which may or may not be citrate (cls.2-9).

54. Similarly, the common specification teaches enhancing stability when using mannitol as a tonicity agent only in formulations that also include a chelating agent. (*See id.* 3:21-29, 5:52-66.) None of the asserted claims other than claim 27 of the '094 Patent, however, requires mannitol with a chelating agent. Even as to claim 27 of the '094 Patent, the chelating agent does not have to be EDTA.

140. I understand that Helsinn may have the opportunity to address so-called secondary considerations relating to obviousness. I reserve the right to respond to any such argument.

Dated: January 6, 2016

J. Broadhead
Dr. Joanne Broadhead