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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC,	)	
Plaintiffs,	)	Civil Action No. 11-3962 (MLC)(DEA)
v.	)	Civil Action No. 11-5579 (MLC)(DEA) (consolidated)
DR. REDDY'S LABORATORIES, LTD., DR. REDDY'S LABORATORIES, INC., SANDOZ, INC., TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES, LTD.,	)	Hon. Mary L. Cooper, U.S.D.J. Hon. Douglas E. Arpert, U.S.M.J.
Defendants.	)	

REPLY EXPERT REPORT OF PATRICK P. DELUCA, PH.D.

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the art cited by Dr. Amidon, taught that one should not study EDTA or a chelating agent until it was "proven" that metal ions catalyzed oxidation of palonosetron. Indeed, because it was well-known that a chelating agent binds metal ions to prevent metal-catalyzed oxidation, the effects of metals and a chelating agent on degradation were often studied together. (*See, e.g.*, DeLuca Report Ex. 11, Connors, at 99-100.) The Syntex documents support this. Specifically, "in the study to determine the effect of metals" during the preformulation studies on palonosetron, Syntex researchers tested "samples with metals or EDTA" " to determine the catalytic effect of metals and the stabilizing effect of EDTA." (Syntex Preformulation Book, ROCHE0010278, 0010282, underlining added.) Notably, Dr. Amidon omits data for parallel experiments on "10 mg/ml with 0.1% EDTA" listed in the same table in the Bonadeo Supplemental Declaration. (Amidon Rebuttal Report ¶ 128.) Third, Dr. Amidon's alleged "teach[ing] away" (Amidon Rebuttal Report ¶ 128) is also contrary to the fact that Syntex researchers concluded, as a POSA would have done so, that "EDTA (0.1%) improved the stability of [palonosetron] at 10 mg/ml in aqueous solution" and proceeded to develop a formulation with EDTA as a stabilizing chelating agent. (Syntex Preformulation Book, ROCHE0010275.)

210. Finally, Dr. Amidon does not disagree with my opinion that "the concentration of EDTA in the claimed formulation would have been obvious." (DeLuca Report ¶ 102.)

E. Expectation of Success

211. As I explained in detail in my opening report (DeLuca Report ¶¶ 105-109), a POSA would have had more than a reasonable expectation of success in making a pharmaceutically stable intravenous solution of palonosetron by using a low concentration of palonosetron, a slightly acidic pH and appropriate amounts of mannitol and EDTA in the formulation. Dr. Amidon does not disagree with the three specific reasons I provided in support

of my opinion. (DeLuca Report ¶¶ 106-108; *see* Amidon Rebuttal Report ¶¶ 133-137.) Dr. Amidon's broad, general statements about the unpredictability in the field of formulation development do not refute my opinion.

212. Moreover, Dr. Amidon does not provide any factual support for his general criticism of my characterization of Syntex's work on the palonosetron IV formulation as "routine development work." (*See* Amidon Rebuttal Report ¶ 135.) Dr. Amidon does not explain why he views the work as anything other than routine. Moreover, Dr. Amidon does not explain how the "confidential information, including clinical information" available to Syntex or Helsinn researchers led to the claimed invention. Importantly, I rely on the prior art and the skill of a POSA to reach my opinion that a POSA would have made a palonosetron formulation as claimed in the patents-in-suit, and would have reasonably expected the formulation to be pharmaceutically stable. I do not rely on any other information, such as the "routine development work" described in the patents-in-suit and recorded by Syntex, to come to my opinion. However, as I made clear (DeLuca Report ¶ 126), the Syntex documents confirm my opinion that the claimed formulation would have been obvious over the prior art.

213. Dr. Amidon appears to confuse the expectation of sufficient pharmaceutical stability with the confirmation of such stability through actual long-term, real-time stability testing. (*See* Amidon Rebuttal Report ¶ 136.) Stability is a property of a particular formulation. Whether a formulation is stable (or unstable) has nothing to do with whether it was tested to be so. Moreover, as taught in the prior art, those working in pharmaceutical development routinely estimated formulation stability through experimentation under stress conditions. (Ex. 20, Connors, Chapter 2.) Thus, a POSA certainly could have had a reasonable expectation of stability without actual stability testing data. Syntex's documents support this. (*See* Syntex

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Formulation Book, ROCHE0008768.) I also note that Helsinn even relied on the "predicted" stability of the Example 13 formulation of the '333 patent to obtain the '724 patent (*see* Ex. 21, p. 8), and Dr. Amidon relies on the same "predicted" stability to support his (erroneous) unexpected results argument. (*See* ¶ 222 below.)

214. Finally, as discussed in my opening report (DeLuca Report ¶¶ 105-109), a POSA would have had a reasonable expectation of stability based on the various prior art references, including Won. Contrary to Dr. Amidon's assertion (Amidon Rebuttal Report ¶ 137), the statements in Won regarding the negative effect of certain impurities on the stability of RG12915 would not by itself have established that a formulation of palonosetron would be unstable. Instead, the statements would have caused a POSA to be mindful of the potential negative effects of such impurities in a palonosetron formulation.

VIII. SECONDARY CONSIDERATIONS

215. I understand that certain "objective" evidence of "secondary considerations," such as "unexpected results" and "commercial success" may be considered in evaluating the obviousness of a claimed invention. In this case, Dr. Amidon asserts certain "unexpected properties of the claimed invention and other objective indicia of nonobviousness" to support his opinions. (Amidon Rebuttal Report ¶ 138.) In my opinion, however, no such evidence of secondary considerations supports the alleged non-obviousness of the claimed palonosetron formulation.

A. The Alleged "Unexpected Efficacy"

216. I understand that for a showing of "unexpected results" to be probative of non-obviousness, it must be established that the claimed invention exhibits an actual, superior

use a chelating agent or EDTA (Amidon Rebuttal Report ¶¶ 101-123), but Syntex researchers did test ETDA during their preformulation studies, even before formulation development. (Syntex Preformulation Book, ROCHE0010282.) Dr. Amidon asserts that a POSA would not have been motivated to use mannitol (Amidon Rebuttal Report ¶¶ 129-132), but Syntex researchers did test mannitol as a tonicifying agent. (Syntex Formulation Book, ROCHE0008766.) Dr. Amidon asserts that a POSA would not have reasonably expected a pharmaceutically stable formulation (Amidon Rebuttal Report ¶¶ 133-137), but Syntex researchers expected that a formulation containing a low palonosetron concentration, EDTA and mannitol at pH 5, "should have an adequate stability of at least two years shelf life at room temperature." (Syntex Formulation Book, ROCHE0008768.) Dr. Amidon asserts that "numerous experiments" or "undue experimentation" would have been required (Amidon Rebuttal Report ¶¶ 119, 124, 134), but Syntex researchers reached the claimed formulation through just a few routine preformulation and formulation screening and optimization studies. (The '724 patent, Examples 1-3; Syntex Formulation Book, ROCHE0008766-68.) All of these facts make clear that Dr. Amidon's opinions are incorrect.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge, information and belief.

Dated: November 21, 2013

Patrick P. DeLuca, Ph.D.