

Filed On Behalf Of: Novartis AG

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

**PAR PHARMACEUTICAL, INC.,
BRECKENRIDGE PHARMACEUTICAL, INC. AND
ROXANE LABORATORIES, INC.,**
Petitioners,

v.

NOVARTIS AG,
Patent Owner

Case IPR2016-00084¹
U.S. Patent 5,665,772

**PATENT OWNER'S MOTION FOR OBSERVATIONS ON
CROSS-EXAMINATION OF WILLIAM L. JORGENSEN, PH.D**

¹ Breckenridge Pharmaceutical, Inc. was joined as a party to this proceeding via a Motion for Joinder in IPR2016-01023; Roxane Laboratories, Inc. was joined as a party via a Motion for Joinder in IPR2016-01102.

I. Yalkowsky Would Not Have Motivated A POSA To Modify Rapamycin To Arrive At Everolimus, Nor Provided A Reasonable Expectation That Everolimus Would Have Increased Water Solubility

At Ex. 2222, page 113, line 19 to page 115, line 6, Dr. Jorgensen testified that that the free energy change (ΔG) for a process such as dissolution is dependent upon the change in entropy (ΔS), enthalpy (ΔH) and temperature (T) as reflected in the thermodynamic formula $\Delta G = \Delta H - T\Delta S$, and a chemical change that results in a more negative value for ΔG will favor dissolution. This testimony is relevant to Petitioners' reliance on Yalkowsky's entropy teachings and assertion that "flexible bonds would have been reasonably expected to increase the internal entropy of fusion as taught by Yalkowsky and favorably influence everolimus's dissolution. ([Ex. 1118] ¶¶88-90; Ex. 1007 at 108 ('there is a regular increase in ΔS_f with increasing chain length'.))" Paper 46 ("Reply") 14. This testimony is relevant because it indicates that when considering the change in free energy of dissolution (ΔG), and whether a given chemical change will increase solubility, it is not sufficient to consider only the change in entropy (ΔS), as *enthalpy* (ΔH) must also be considered.

At Ex. 2222, page 120, line 13 to page 122, line 10, Dr. Jorgensen testified that chemically modifying a compound may result in an increase in entropy but a decrease in water solubility. This testimony is relevant to Petitioners' assertion that "increasing internal entropy had been shown to increase calculations of ideal

solubility and result in increased actual measured solubility.” Reply 16. This testimony is relevant because it contradicts Petitioners’ suggestion that an increase in internal entropy will necessarily lead to an *increase* in water solubility, and instead shows that an increase in internal entropy can lead to a *decrease* in water solubility. *See also* Ex. 2091, Tr. 47:15-48:22 (discussing interplay between entropic and enthalpic effects).

At Ex. 2222, page 120, lines 4 to 9 and page 116, lines 14 to 25, Dr. Jorgensen admitted that Yalkowsky does not discuss the impact of adding flexible groups on *enthalpy*, and agreed that in “an ideal solution, the focus would be only entropy of solution if you’re looking at the free energy change” because “the enthalpy change in mixing is zero.” This testimony is relevant to Petitioners’ reliance on Yalkowsky, and assertion that Yalkowsky’s teachings about the effect of entropy on dissolution are not limited to ideal solutions. Reply 15-16. This testimony is relevant because it shows that while an increase in entropy may result in an increase in ideal solubility (because the change in enthalpy, ΔH , is zero in an ideal solution), the same is not true in a non-ideal solution because enthalpy must also be considered.

At Ex. 2222, page 117, line 4 to page 118, line 16, Dr. Jorgensen testified that the process described in Yalkowsky’s Figure 2 concerns entropy, and does not concern enthalpy. This testimony is relevant to Petitioners’ assertion that Figure 2

is not limited to ideal solutions. Reply 15-16; Ex. 1118 ¶ 82. This testimony is relevant because it confirms that Yalkowsky's Figure 2 does not account for a change in enthalpy upon dissolution, and enthalpy is a factor that a person of ordinary skill in the art ("POSA") would consider when evaluating solubility in a non-ideal solution (*see supra*).

At Ex. 2222, page 120, lines 10 to 12, Dr. Jorgensen testified that the effect of adding a flexible chain on *enthalpy* is not independent of the solvent (*i.e.*, it is solvent-dependent). This testimony is relevant to Petitioners' assertion that the "favorable effect [on *entropy* of a flexible chain upon dissolution] is independent of the solvent." Reply 15-16; Ex. 1118 ¶ 82. This testimony is relevant because it shows that the impact of adding a flexible chain is solvent-dependent where the solution is non-ideal, because *enthalpy* must also be considered.

At Ex. 2222, page 115, line 7 to page 116, line 3, Dr. Jorgensen testified (consistent with Petitioners' counsel's objection), that enthalpy of solution was not an issue discussed in his supplemental declaration, and that he did not cite any references that suggest a more polar compound would have a more negative enthalpy of solution. This testimony is relevant because it goes to the weight and credibility of Dr. Jorgensen's testimony about water solubility and his assertion that more polar compounds would have a more negative enthalpy of solution. Ex. 2222, Tr. 115:7-21.

At Ex. 2222, page 124, line 18 to page 127, line 13, Dr. Jorgensen testified that that the trend discussed in paragraphs 97-99 of his supplemental declaration (Ex. 1118), that solubility of alkyl *p*-aminobenzoates increased with increasing chain length, was based on calculated ideal solubilities and solubility in methanol, ethanol and 1-propanol, not in water; Dr. Jorgensen further testified that the trend would be different in water. This testimony is relevant to Petitioners' assertion that "ideal solubility is premised on basic thermodynamic concepts that apply to all systems . . . and a POSA would have understood the same qualitative effects apply in real and ideal systems. ([Ex. 1118] ¶¶13, 92-99.)" Reply 16. This testimony is relevant because, as Dr. Jorgensen testified, the "qualitative effect" on solubility of increasing chain length will vary depending on the solvent.

At Ex. 2222, page 133, line 7 to page 134, line 11, Dr. Jorgensen agreed that Yalkowsky 1972 (Ex. 2219) examined the *water solubility* of alkyl *p*-aminobenzoates (the same compounds discussed in Yalkowsky (Ex. 1007) Table III, Schwartz (Ex. 1117), and Ex. 1118 ¶¶ 97-99 (*see* Ex. 2222, Tr. 130:19-131:19)), and reported in Figure 2 that as hydrocarbon chain length increased (and therefore entropy increased), water solubility decreased, which trend is the opposite of that reported in Table II of Schwartz in methanol, ethanol, or 1-propanol, or as calculated using ideal solubility calculations. This testimony is relevant to Petitioners' assertion that "increasing internal entropy had been shown

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