

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARGENTUM PHARMACEUTICALS LLC,
Petitioner

v.

ALCON RESEARCH, LTD.
Patent Owner

Patent No. 8,268,299

Issue Date: September 18, 2012

Title: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

Inter Partes Review No.: IPR2017-01053

**PETITIONER'S RESPONSE TO PATENT OWNER'S MOTION FOR
OBSERVATIONS ON CROSS-EXAMINATION OF PETITIONER'S
REPLY WITNESS DR. ERNING XIA**

Petitioner Argentum Pharmaceuticals LLC (“Petitioner”) hereby responds to Alcon Research Ltd.’s motion for observations on the deposition of Petitioner’s expert Dr. Erning Xia (Paper 43, hereafter “Mot.”). Office Patent Trial Practice Guide, 77 Fed. Reg. 48756 at 48767-68 (August 14, 2012).

Observation #1: Patent Owner’s assertion that Dr. Xia’s testimony contradicts Petitioner’s argument that a POSA “would have arrived at the claims of the ‘299 Patent via routine optimization” is unsupported. First, Counsel’s final question to Dr. Xia was a compound question (“Is that the only place the POSA may have ended up *or* could the POSA have ended up at...different formulation?”), such that Dr. Xia’s answer in the affirmative could just as easily be understood to be confirming the first part of the question versus the second. Counsel did not clarify which part of this question Dr. Xia was answering. ALCON2166, 107:7-11. Second, there is no foundation in Counsel’s question for what was meant by “different formulation.” The combined cited art provides a variety of (different) obvious formulations meeting the claimed limitations. *See, e.g.,* Pet., 15 and Reply, 12 (arguing that Chowhan discloses a range of borate/polyol concentrations falling within the claimed range). These observations are relevant because they do not support Patent Owner’s characterization of Dr. Xia’s testimony as contradicting Petitioner’s routine optimization argument.

Observation #2: Patent Owner’s assertions that Dr. Xia is not a microbiologist and does not know if zinc is a necessary micronutrient for bacterial growth is taken out of context and not relevant to Dr. Xia’s qualification to opine on Alcon’s argument that “the POSA would affirmatively be concerned that zinc compositions with less zinc than the 0.48 mM in Xia’s Example 18 would fail PET.” In making this assertion Patent Owner overlooks Dr. Xia’s over 30 years of experience in not just ophthalmic formulations (110 patents, 36 publications), but in ophthalmic preservative systems, including the very zinc preserved ophthalmic formulations of the Xia reference, of which he is an inventor. EX1002 ¶¶6-13; EX1015. Patent Owner overlooks Dr. Xia’s clarification that zinc “by itself” is not a foodstuff (ALCON2166 50:15-19) in an ophthalmic formulation. *Id.* 40:7-14. Patent Owner further overlooks Dr. Xia’s testimony (*id.*, 49:19-50:6, 51:2-6; EX1093, ¶¶13-24) and Dr. Zhanel’s testimony (Alcon’s own microbiology expert) (EX1048, 49:6-9; 50:8-10, 50:13-16; 55:17-22; 114:15-21) that non-ophthalmic compositions (such as those in Winslow, McCarthy, and Zeelie) cannot predict PET for ophthalmic compositions and a 48 hour test cannot predict PET. Finally, Patent Owner overlooks their own admission that Xia teaches zinc concentrations lower than 0.48 mM and that preservation may be achieved “using zinc and ‘less than a preservative-effective amount of a primary preservative agents’ ...” (POR, 9, 17; ALCON2023, ¶¶29, 60; ALCON2025, ¶¶22, 26), which contradicts Alcon’s

present argument, and supports Petitioner’s argument that “a POSA would combine zinc with another preservative agent—in this case, the borate-polyols as taught by Chowan and already present in both the Xia and Schneider formulations.” Reply, 8 (citing EX1093, ¶¶28-38).

Observation #3: Patent Owner mischaracterizes Dr. Xia’s testimony regarding EX1093, ¶24. Paragraph 24 states “I believe a POSA would avoid high zinc concentrations knowing zinc at 0.25 w/v% is an astringent and use Xia’s express teaching of zinc concentrations as low as 0.074 mM to determine an optimum zinc concentration in an ophthalmic solution that passes standard PET.” EX1093, ¶24. Dr. Xia’s testimony that “high” in the sentence refers to 0.25 w/v% and that 0.25 w/v% is not in the zinc concentration range taught by Xia (ALCON2166, 53:21-25) does not contradict Petitioner’s argument. Rather, Dr. Xia’s testimony is consistent with Petitioner’s argument that “a POSA would have been concerned with using too high a level of zinc, and would therefore have engaged in optimization to find the lowest suitable zinc concentration.” Reply, 5 (citing EX1093, ¶12). Dr. Xia’s testimony is also consistent with Dr. Majumdar’s testimony that a POSA would avoid zinc concentrations that cause astringency (*i.e.*, 0.25 w/v%) and that all else being equal, a POSA would opt for the lowest preservative concentration that passes PET (EX1045, 51:24-52:10, 79:9-16; *see also* 1093, ¶12).

Observation #4: Patent Owner mischaracterizes Dr. Xia’s testimony concerning the phrase “are useful” in EX1093, ¶11 in relation to 0.001% and 0.005% zinc concentrations as he testified the phrase “means it *may* need some help from other ingredients.” ALCON2166, 73:1-5 (emphasis added). Patent Owner also overlooks Dr. Zhanel’s testimony that “the POSA cannot find a very specific statement that says do not go lower with zinc than 0.0065 percent if you expect to pass preservative efficacy” (EX1048, 123:12-124:14), which contradicts Patent Owner’s argument. Furthermore, Patent Owner overlooks their own admission that Xia teaches zinc concentrations lower than 0.48 mM and that preservation may be achieved “using zinc and ‘less than a preservative-effective amount of a primary preservative agents’ ...” (POR, 9, 17; ALCON2023, ¶¶29, 60; ALCON2025, ¶¶22, 26), which contradicts Patent Owner’s current argument and supports Petitioner’s argument that “a POSA would combine zinc with another preservative agent—in this case, the borate-polyols as taught by Chowan and already present in both the Xia and Schneider formulations.” Reply, 8 (citing EX1093, ¶¶28-38).

Observation #5: Alcon’s assertion that Dr. Xia’s testimony demonstrates that the POSA would not have considered borate-polyol complexes to fall within Xia’s definition of “primary preservative agent” mischaracterizes the testimony

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