IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INNOPHARMA LICENSING, INC., INNOPHARMA LICENSING LLC,
INNOPHARMA INC., INNOPHARMA LLC,
MYLAN PHARMACEUTICALS INC., and MYLAN INC.
Petitioner,

v.

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB, INC., and
BAUSCH & LOMB PHARMA HOLDINGS CORP.
Patent Owner.

Case IPR2015-00902 (Patent 8,669,290 B2)
Case IPR2015-00903 (Patent 8,129,431 B2)[1]

REPLY DECLARATION OF PAUL A. LASKAR, PH.D.

[1] A word-for-word identical paper has been filed in each proceeding identified in the heading. IPR2015-01871 has been joined with IPR2015-00903 and includes Petitioners Lupin Ltd. and Lupin Pharmaceuticals Inc. in addition to the parties identified above.

I. List of documents I considered in formulating my opinion in this declaration

1. In formulating my opinion below, I have considered all documents cited in this Declaration.

II. The Disclosure of Fu includes Tyloxapol

2. Patent Owners' experts take the position that Fu does not disclose tyloxapol to a skilled artisan. (EX2082, ¶¶ 92, 94, 180 / ¶¶ 84, 86, 136; EX2105, ¶ 94 / ¶ 92).[2] I disagree. Fu teaches that the "nonionic ethoxylated octylphenol surfactant is an octylphenoxypoly(ethyleneoxy)ethanol with a mole ratio of ethylene oxide to octylphenol of between 3:1 and 40:1." (*See, e.g.*, EX1011, Claim 3).[3] Therefore, Fu teaches a series of ethoxylated octylphenol surfactant. (*See also* EX1079, 112:7-16 (Patent Owner's expert admitting that given these mole ratios, Fu discloses a "series of octoxynols")).

3. Tyloxapol falls within the series disclosed by Fu. The mole ratio of ethylene oxide to octylphenol of tyloxapol is 8-10 to 1. (*See* EX2105, ¶ 86 / ¶ 84

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[2] Citations to the Declarations of Dr. Williams and Dr. Davies are to the paragraph number(s) to their declarations in IPR2015-00902, followed by the paragraphs number(s) to their declarations in IPR2015-00903, with a slash separating the two.

[3] Citations to the exhibits of record will be to the exhibit numbers in IPR2015-00902 unless stated otherwise.

(providing n and m values of tyloxapol);[4] EX1091, col. 1, lines 45-61 ("A preferred compound of this group is the product containing **ten ether groups per p-tertiary-octylphenol nucleus** which is known under the brand names, Superinone and Triton WR-1339, chemically as oxyethylated tertiary octylphenol formaldehyde polymer or p-isooctylpoly-oxyethylenephenol formaldehyde polymer, and, **generically as tyloxapol**") (emphasis added). Thus, a skilled artisan would conclude that tyloxapol falls within the disclosure of Fu.

III. Tyloxapol is an Antioxidant

4. I understand that Patent Owners' experts have stated that since Ogawa Example 6 is a bromfenac formulation, the bromfenac in the solution is susceptible to oxidation. (EX2105, ¶ 74 / ¶ 72) ("Ogawa Example 6 is a bromfenac formulation, and bromfenac is susceptible to oxidation"). Moreover, Patent Owners' experts have identified the surfactant polysorbate 80 as the source of bromfenac's degradation in Ogawa providing a motivation to replace the

[4] The values reported by Dr. Davies are consistent with Schott (EX1019 / EX1024). Using Schott, which states that "[t]yloxapol is essentially an oligomer of octoxynol 9" including explaining that "[d]espite the methylene bridges, it has practically the same hydrophilic-lipophilic balance as octoxynol," the mole ratio of ethylene oxide to octylphenol of tyloxapol is 9.6 to 1.

surfactant. (*Id*. ("A person of ordinary skill in the art would expect bromfenac to degrade in the presence of . . . polysorbate 80.")).[5]

5. I made a similar observation about the liability of using polysorbate 80 and why the skilled artisan would have been motivated to replace polysorbate 80 with an alternative non-ionic surfactant (*i.e*., tyloxapol) that did not generate peroxides, and its resulting improvement on stability of bromfenac formulations of Ogawa. (EX2114, 183:3-7 ("[I]n example 6 by virtue of replacing polysorbate 80 with its peroxides with an alternative non-ionic surfactant that does not have the liability of peroxides would, in fact, likely enhance the stability of the composition."); *see also* EX2114, 157:18-22 ("And given the presence of peroxides in polysorbate 80 and their lack in tyloxapol, this indicates that tyloxapol, in this composition because its simpler, would be the favorite.").

6. I also explained during my deposition, in reference to the data presented in Yasueda, tyloxapol, in addition to being a non-ionic surfactant, also had antioxidant properties: "it's apparent from the composition that BHT is not present in formulations A, B, and C indicating that tyloxapol had no need for an

[5] In that same section, Dr. Davies also takes the position that tyloxapol would also lead to the generation of peroxides and hydroperoxides. I disagree, and I will address Dr. Davies' contentions later in this declaration.

antioxidant. ***And that comes not as any surprise to me. . .*** ." (EX2114, 157:13-18 (emphasis added)).

7. Knowing that polysorbate 80 was the cause of oxidative degradation, the skilled artisan would have replaced the polysorbate 80 with another non-ionic surfactant that did not share polysorbate 80's liability. The skilled artisan would have known that tyloxapol, like polysorbate 80, is not only a non-ionic surfactant commonly used in ophthalmic solutions but, unlike polysorbate 80, it also has antioxidant properties. As I explained during my original deposition, using a non-ionic surfactant without the liability of polysorbate 80 would "enhance the stability of the composition." (EX2114, 183:1-7).

8. Put another way, polysorbate 80 is an oxidizing agent (whereas tyloxapol is an antioxidant).[6] Moreover, Patent Owner's experts agree with my conclusions that polysorbate 80 generates peroxides which negatively impacts the stability of Example 6 of Ogawa, and that the stability of the bromfenac solutions disclosed in Ogawa can be improved by replacing polysorbate 80. (EX2105, ¶ 74 / ¶ 72).

[6] Polysorbate 80 is an oxidizing agent because it degrades to produce peroxides and hydroperoxides. (*See also* EX2105, ¶ 74 / ¶ 72).

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