IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SENJU PHARMACEUTICAL CO., LTD., BAUSCH & LOMB INCORPORATED and BAUSCH & LOMB PHARMA HOLDINGS CORP., Plaintiffs, v. LUPIN, LTD. and LUPIN PHARMACEUTICALS, INC., Defendants.	Civil Action No. 1:14-cv-00667 (JBS)(KMW) Civil Action No. 1:14-cv-04149 (JBS)(KMW) Civil Action No. 1:14-cv-05144 (JBS)(KMW) Civil Action No. 1:15-cv-00335 (JBS)(KMW)
INNOPHARMA LICENSING, INC., INNOPHARMA LICENSING, LLC, INNOPHARMA, INC. and INNOPHARMA, LLC, Defendants.	Civil Action No. 1:14-cv-06893 (JBS)(KMW) Civil Action No. 1:15-cv-03240 (JBS)(KMW) (Consolidated Actions)

REPLY EXPERT REPORT OF STEPHEN G. DAVIES, D.Phil.

I. BACKGROUND AND QUALIFICATIONS

1. I, Stephen G. Davies, D.Phil., submit this reply report at the request of Plaintiffs Senju Pharmaceutical, Co., Ltd., Bausch & Lomb Incorporated, and Bausch & Lomb Pharma Holdings Corp. as an expert in the field of organic chemistry and medicinal chemistry. My qualifications in these areas, as well as other areas, are summarized in my responsive expert report dated January 29, 2016, and established by my *curriculum vitae*, attached as Appendix B to my responsive expert report, and list of publications, attached as Appendix C to my responsive expert report.

2. I am submitting this reply report in response to the responsive report of Dr. Clayton H. Heathcock, dated February 12, 2016.

3. I reserve the right to further address Dr. Heathcock's statements, opinions and conclusions at a later time. To the extent Dr. Heathcock provides additional statements, opinions or conclusions, including any rebuttal or reply reports, I may offer further opinions.

II. INFORMATION CONSIDERED

4. In forming the opinions expressed in this expert report, I had available the documents cited herein, the documents cited in my responsive expert report as well as the publications listed on my *curriculum vitae* and publications list. I have also reviewed the responsive expert report of Dr. Heathcock. I also base this opinion on my professional and academic experience in the areas of organic chemistry and medicinal chemistry. I reserve the right to testify about these materials and experience. To the extent I am provided additional documents or information, including any expert reports produced by Lupin or InnoPharma, I may offer further opinions. In addition to these materials, I may consider additional documents and information in forming any rebuttal opinions. Additionally, I may prepare demonstratives to illustrate any opinions I may present.

III. STATEMENT OF OPINIONS EXPRESSED AND BASES AND REASONS THEREFOR

A. A Person of Ordinary Skill in the Art

5. My discussion regarding the person of ordinary skill in the art was set forth in my responsive expert report, and nothing in Dr. Heathcock's report has changed any of my opinions stated in my responsive expert report.

6. Dr. Heathcock states "I note that the patents-in-suit are directed to pharmaceutical formulations and formulation science. While Dr. Lawrence's definition of the POSA directly addresses this field (requiring a 'pharmaceutical scientist'), Dr. Davies' definition misses the mark in focusing on chemistry as the relevant field. This narrow focus on chemistry in his

definition of the POSA may account, to some extent, for Dr. Davies' misplaced focus in rendering his opinions on the structural minutiae of various pharmaceutical formulation excipients or ingredients. Because Dr. Davies, focuses on the chemistry, however, I respond to those chemistry-based arguments, in this report. Nevertheless, my opinions would not change, regardless of which definition of a POSA is used." (Heathcock Responsive Report at ¶ 31.) I disagree with Dr. Heathcock's statements. As set forth in my responsive report, "[a]s of January 21, 2003, a person of ordinary skill in the art would have had at least a Bachelor's degree in a field such as pharmaceutical chemistry, chemistry or a related discipline with about three to five years of work experience in this area, or a comparable level of education and training." (Davies Responsive Report at ¶ 11.) My definition encompasses "a pharmaceutical scientist" from Dr. Lawrence's definition, with which Dr. Heathcock agrees. (Heathcock Responsive Report at ¶ 29.) My definition is in fact broader than Dr. Lawrence's, including "related disciplines" such as formulation science.

B. Non-steroidal Anti-Inflammatory Drugs

7. Dr. Heathcock describes and depicts the structures of several non-steroidal anti-inflammatory drugs ("NSAIDs"), concluding that "all of these NSAID compounds - bromfenac, flurbiprofen, diclofenac, ketorolac - have a carboxyl moiety." (Heathcock Responsive Report at ¶¶ 32-37.) As discussed in my responsive report, bromfenac is structurally and chemically dissimilar to diclofenac, ketorolac and flurbiprofen. (Davies Responsive Report at ¶¶ 16-44.) The physical, chemical and biological properties of molecules containing multiple functional groups do not depend solely on the characteristics of one of those functional groups. (*Id.* at ¶ 16.) These properties depend on complex interactions between all the functional groups present in the molecule and their disposition relative to each other, and it is a gross oversimplification to

suggest that all carboxylic acids will behave similarly or will have similar properties. (*Id.* at ¶¶ 16-44.)

C. Surfactants

8. Dr. Heathcock describes the properties of surfactants generally, recognizing that "non-ionic surfactants may have some differences in their compositions and three-dimensional structures," and identifying critical micelle concentration ("CMC") as "a unique characteristic of each surfactant." (Heathcock Responsive Report at ¶¶ 38-41.) As discussed in my opening report, non-ionic surfactants, including polysorbate 80, tyloxapol, Octoxynol 9, and Octoxynol 40, are structurally and chemically diverse and therefore possess diverse characteristics, including molecular weight and CMC. (Davies Responsive Report at ¶¶ 62-79.) The CMC, which Dr. Heathcock characterizes as a unique characteristic of each surfactant, varies significantly among polysorbate 80, Octoxynol 9, Octoxynol 40 and tyloxapol. (*Id.* at ¶¶ 67, 75.) As discussed in my opening report, a person of ordinary skill in the art would expect these differences in CMC to lead to significantly different functional and chemical properties, including solubilizing properties. (*Id.* at ¶ 64.) Indeed, Dr. Lawrence relies on the solubilizing properties of surfactants for her position on motivation to combine various teachings of unrelated documents in the art for allegedly improving the physical stability of an ophthalmic solution containing an acidic NSAID and BAC. (*See, e.g.*, Lawrence Opening Report at ¶ 69.)

9. Dr. Heathcock states that "[i]n addition to being a surfactant, tyloxapol was reported to be a potent antioxidant, which means it inhibits the oxidation of other molecules," citing U.S. Patent No. 5,474,760 ("the '760 patent"). (Heathcock Responsive Report at ¶ 42.) As discussed further below, I disagree with Dr. Heathcock's statement. The '760 patent on which Dr. Heathcock relies is irrelevant to tyloxapol's use in aqueous bromfenac ophthalmic solutions.

D. Dr. Heathcock Has Not Established That a Precipitate Will Form Between an NSAID such as Bromfenac and BAC

10. Dr. Heathcock states that "[b]ased on the teachings of the prior art, a POSA would have known that NSAIDs were known to form complexes with quaternary ammonium compounds while in solution, causing them to precipitate from solution. It is most likely that these insoluble complexes between BAC and acidic NSAIDs are salts where the anion is the NSAID carboxylate and the cation is the BAC ammonium ion." (Heathcock Responsive Report at ¶ 45.) Dr. Heathcock repeats this assertion throughout his report. I disagree with Dr. Heathcock's statements. As discussed in my responsive report, Dr. Lawrence and now Dr. Heathcock fail to consider the significant structural and chemical differences among NSAIDs and the unpredictability of a system containing an NSAID and BAC. Moreover, an NSAID and a quaternary ammonium compound cannot form a complex, and can only potentially form a salt. A complex is a species formed from two or more not necessarily charged fragments held together by more than simple electrostatic charges, whereas a salt is a mixture of positive cations and negative anions held together by purely electrostatic charges where the overall charge is zero. (Davies Responsive Report at ¶ 14, n.1.) It makes no sense, therefore, to state that "NSAIDs were known to form complexes with quaternary ammonium compounds while in solution."

11. Dr. Heathcock further states that "a POSA would have been concerned that a complex would form in a solution containing the NSAID bromfenac sodium and the quaternary ammonium compound benzalkonium chloride ("BAC"), causing the compounds to precipitate from solution." (Heathcock Responsive Report at ¶ 47.) I disagree with Dr. Heathcock's statements for all the reasons discussed below and in my responsive report. Dr. Heathcock has failed to identify any evidence that a precipitate forms between bromfenac and BAC in an aqueous solution. Moreover, as discussed above, it makes no sense to state that "a complex

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