UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MICRO LABS LIMITED AND MICRO LABS USA INC.,
Petitioner,

v.

SANTEN PHARMACEUTICAL CO., LTD. AND
ASAHI GLASS CO., LTD.,
Patent Owner.

Case IPR2017-01434
U.S. Patent No. 5,886,035

SUPPLEMENTAL DECLARATION OF TIMOTHY L. MACDONALD, PH.D.

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I, Timothy L. Macdonald, Ph.D., declare and state as follows:

I. INTRODUCTION

1. I am Professor of Chemistry, and former Chair of Chemistry, at the University of Virginia ("UVA"). I also hold a secondary appointment as Professor of Pharmacology at UVA.

2. I have been retained on behalf of Patent Owners Santen Pharmaceutical Co., Ltd. and Asahi Glass Co., Ltd. (together, "Patent Owner") as an independent expert consultant in the above-referenced *inter partes* review ("IPR") proceeding, to provide information and opinions on the teachings of the prior art and the state of the art, as relevant to the issued claims of U.S. Patent No. 5,886,035 ("the '035 Patent"). Ex.1001.

3. I previously submitted a written declaration on these topics, which was filed as Ex.2001. I hereby incorporate my previous declaration into this declaration.

4. For purposes of this declaration, I have been asked to explain, as of December 26, 1996, how a POSITA developing prostaglandin analogs for IOP-lowering would have viewed an initial increase in IOP caused by a candidate compound.

5. I have also been asked to consider whether objective secondary considerations of nonobviousness (for example, commercial success, copying,

unexpected results, long-felt but unmet need, and failure of others) support the nonobviousness of the claims of the '035 Patent.

6. My opinions in this Declaration are based on documents I have reviewed in connection with this proceeding, and are further informed by my knowledge and experience, including my decades of experience in medicinal chemistry and molecular pharmacology. I have also relied on the Supplemental Declaration of Robert D. Fechtner, M.D. (Ex.2029), which I understand is also being submitted in this proceeding. An updated list of the documents and materials that I considered in connection with the development of my opinions set forth in this (and my previous) declaration is attached hereto as Exhibit B.

II. AN INITIAL INCREASE IN IOP WAS A SERIOUS FLAW FOR A POTENTIAL IOP-LOWERING DRUG

7. As of December 26, 1996, a POSITA would have recognized that an initial increase in IOP, as was reported for Compound C of Klimko, was a serious deficiency in the context of a potential IOP-lowering drug. A POSITA at the time would also have understood that the initial increase in IOP could not be easily overcome, for example, by reducing the dose. Rather, a POSITA would have expected that decreasing the administered dose of Compound C would have the effect of decreasing the overall efficacy of the drug. This is because the initial increase in IOP is part of a biphasic response to Compound C; the first phase is a

hypertensive phase where IOP is increased, and the second phase is a hypotensive phase where IOP is reduced. *See, e.g.,* Camras *et al*., "Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits," *Invest. Ophthalmol. Vis. Sci.* 16:1125-1134 (1977) ("Camras 1977") (Ex.2003), 2. Given that Klimko does not provide dose-response curves for Compound C, a POSITA would have expected similar dose-response curves for both phases of the response to Compound C. While the unacceptable initial increase in IOP could potentially have been reduced by a low enough dose, a POSITA would have expected that the later IOP reduction would have been reduced as well. For example, in Camras 1977 (Ex.2003), 4, $PGF_{2\alpha}$ was shown to exhibit an initial IOP increase after administration. Although the initial IOP increase was mitigated by drastically lowering the dose of $PGF_{2\alpha}$, the IOP-lowering activity was compromised at those lower doses. *Id*. At a 200 µg dose, $PGF_{2\alpha}$ provided IOP-lowering activity for at least about a full day, but there was a significant initial increase in IOP after administration. *Id*. At 50 µg $PGF_{2\alpha}$, the initial increase in IOP was not reduced. *Id*. At 5 µg $PGF_{2\alpha}$, the initial increase in IOP was reduced, but the area under the curve of the IOP-lowering was dramatically reduced, and the duration of efficacy was limited to 15 hours or less (rather than at least about a full day at 50 µg and 200 µg). *Id*. In my experience, a POSITA always favored development of compounds that do not increase IOP over compounds that do

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