IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Mylan Pharmaceuticals Inc., Petitioner

v.

Nissan Chemical Industries Ltd.
Patent Owner

U.S. Patent No. 5,856,336 to Fujikawa *et al.*
Issue Date: January 5, 1999
Title: Quinoline Type Mevalonolactones

Inter Partes Review No.: IPR2015-01069

Declaration of Roger F. Newton, Ph.D. in Support of Mylan Pharmaceuticals Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 5,856,336

I. INTRODUCTION

1. I am over the age of eighteen (18) and otherwise competent to make this Declaration.

2. I have been retained as an expert witness on behalf of Petitioner for the above-captioned *inter partes* review ("IPR"). I am being compensated for my time in connection with this IPR at my standard consulting rate, which is $700 per hour. My compensation does not depend in any way on the outcome of this IPR.

3. It is my understanding that the Petition for IPR in this matter involves U.S. Patent No. 5,856,336 to Fujikawa *et al.* ("the '336 patent") (EX1001). It is also my understanding that the records of the USPTO indicate that the current owner of the '336 patent is Nissan Chemical Industries Ltd. ("Nissan").

4. Claim 1 of the '336 patent depicts a compound, which has a 4-fluorophenyl group, a quinoline ring scaffold, and what I have been informed the Patent Owner claims is a cyclopropyl substituent at the 2 position represented by "Δ."[1] This compound, which is in its calcium salt form, is also known as pitavastatin calcium salt. Claim 1 is reproduced below:

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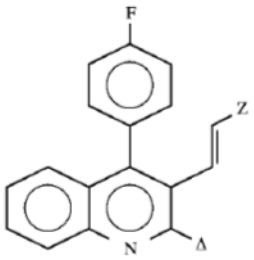
[1] Solely for the purpose of this Declaration and my analysis of the prior art, I will accept the Patent Owner's interpretation.

1. A compound of the formula,



[A]

Z = —CH(OH)—CH2—CH(OH) —CH2—COO.1/2Ca.

(The ’336 patent (EX1001) at col. 32, ll. 21-36).

Claim 1 is not directed to any particular optical isomer. Rather, a person of ordinary skill in the art as to the ’336 patent (“POSA”) would understand that all optical isomers and mixtures thereof are encompassed by the claim.

5. Claim 2 is drawn to methods of using the compound of Claim 1 to reduce hyperlipidemia, hyperlipoproteinemia, or atherosclerosis and is reproduced below:

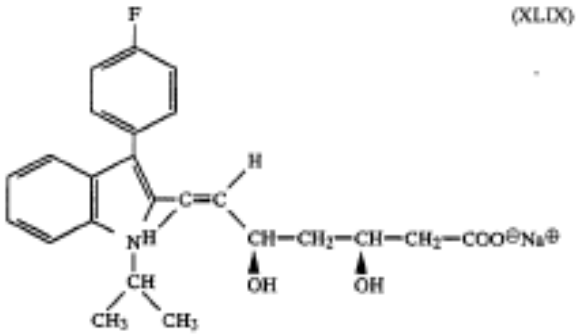
> 2. A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of formula A as defined in Claim 1.

(The ’336 patent (EX1001) at col. 32, ll. 37-40).

6. In preparing this Declaration, I have reviewed the ’336 patent and its prosecution history as well as each of the documents cited in this Declaration and cited in the IPR Petition. In arriving at my opinions, I have relied upon my

experience in the relevant art and have considered the point of view of a POSA, as defined below.

7. It is my opinion that, during the relevant time period, a POSA would have selected the prior art compound shown below as the lead compound:



(U.S. Patent No. 4,739,073 ("the Kathawala '073 patent") (EX1010) filed March 4, 1985, and published April 19, 1988, at col. 52, ll. 27-40).

8. This compound is also known as fluvastatin. The prior art at the relevant time showed that fluvastatin possessed excellent *in vitro* activity. (*See* "the Kathawala '073 patent" (EX1010) at col. 33, ll. 11-43). This compound also demonstrated relatively high activity for *in vivo* cholesterol biosynthesis inhibition. *Id.* The compound was disclosed as lowering several lipid parameters in animals and was reported to be in human clinical trials by at least 1987. (*See* the Kathawala Abstract, EX1009, available at the University of Michigan Chemistry Library on July 29, 1987; the Engstrom Abstract, EX1011, first library stamp December 22, 1987.

9. In addition, competing researchers recognized fluvastatin as one of only 5 HMG-CoA reductase inhibitors that had proceeded to clinical trials and was "particularly interesting." (Tobert, EX1012, available at University of Minnesota Biomedical Library September 11, 1987, pages 534-535; Lee, EX1013, available at the National Library December 2, 1987, page 444 ("particularly interesting")). The POSA also would have understood that fluvastatin was many times more active than two of the other four HMG-CoA reductase inhibitors in clinical trials *in vivo*. (*See* the Kathawala '073 patent, col. 32, l. 53-col. 33, l. 11; col. 33, ll. 50-62).

10. It was known by 1987 that HMG-CoA reductase inhibitors were useful in lowering cholesterol, a risk factor in coronary artery disease. Several major pharmaceutical groups were actively researching these compounds. Thus, the prior art would have motivated a POSA to select fluvastatin as a lead compound for further modification.

11. In considering further modifications, the POSA would have considered the logical structural avenues available to further optimize the compound. Within fluvastatin, both the 4-fluorophenyl group (boxed in green) and isomeric side chain (boxed in blue) reflected the product of prior efforts to optimize structural groups in comparison to the early-generation statin molecules (*i.e.*, compactin and mevinolin):

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