UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ROXANE LABORATORIES, INC.,
Petitioner,

v.

VANDA PHARMACEUTICALS INC.,
Patent Owner.

Case IPR2016-00690
Patent No. 9,138,432

DECLARATION OF FREDERICK PETER GUENGERICH, Ph.D.

June 7, 2016

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I. TASK AND SUMMARY OF OPINIONS

1. I have been retained by Paul, Weiss, Rifkind, Wharton & Garrison LLP, counsel for Vanda Pharmaceuticals Inc. ("Vanda"), to provide my expert testimony in this case.

2. I have been asked to respond to the factual allegations set forth in Roxane's petition for *inter partes* review of claim 1 of U.S. Patent No. 9,138,432 ("the '432 Patent"), including the opinions set forth in the declaration of Roxane's expert, Dr. David Fogelson (Exhibit 1003).

3. I disagree with Roxane and Dr. Fogelson that claim 1 of the'432 Patent is obvious. Roxane and Dr. Fogelson's opinions focus on only isolated portions of the prior art and leave out the prior art evidence that teaches away from the invention claimed in the '432 Patent.

4. Roxane and Dr. Fogelson's opinions are premised on statements in the prior art that iloperidone is metabolized by an enzyme, CYP2D6, *in vitro*. Roxane and Dr. Fogelson, however, ignore the prior art teachings that CYP2D6 metabolism is <u>not</u> significant for iloperidone's metabolism *in vivo*. Based on the prior art as a whole, a person of ordinary skill in the art at the time of the invention

of the ’432 Patent would not have been motivated to study the effect of CYP2D6 inhibition on any side effects, including iloperidone-induced QT prolongation, as iloperidone was not understood to be significantly metabolized by CYP2D6 *in vivo* by skilled artisans in 2004.

5. Moreover, Roxane and Dr. Fogelson overlooked the teachings of the prior art that, as recognized by the Patent Office during its original examination of the ’432 Patent, make clear that the necessary dosage adjustments to minimize the risk of side effects were unpredictable. Based on the entirety of the prior art, a person of ordinary skill in the art would not have had a reasonable expectation that administering 12 mg/day of iloperidone to patients being treated with fluoxetine and administering 24 mg/day of iloperidone to patients who are not treated with fluoxetine would reduce the risk of QT prolongation.

II. PROFESSIONAL BACKGROUND QUALIFICATIONS

6. I am the Tadashi Inagami Professor of Biochemistry at Vanderbilt University School of Medicine (Nashville, Tennessee). I was appointed Assistant Professor of Biochemistry in 1975, and was promoted to Associate Professor in

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