

March 9, 2010

Securities and Exchange Commission  
Division of Corporate Finance  
100 F Street, N.E.  
Washington, D.C. 20549

Attention: Ms. Nandini Acharya

Re: DEF 14A  
Filed March 13, 2009  
File No. 000-30111

Dear Ms. Acharya:

On behalf of Lexicon Pharmaceuticals, Inc., we submit the following additional response to the written comment received on January 25, 2010 from the Securities and Exchange Commission's staff with respect to Lexicon's definitive proxy statement for Lexicon's 2009 annual meeting. Your comment and our response to that comment are set forth below.

**DEF 14A**

Executive and Director Compensation  
Compensation Discussion and Analysis, page 24

1. We note your response to our prior comment 4 and your proposed additional disclosure regarding individual goals. You indicate that individual goals consist principally of the expected individual contributions of each executive officer towards the achievement of the year's corporate goals. To the extent such expected individual contributions are pre-determined and linked to corporate goals, please describe each goal and include an assessment of whether each executive met his or her expected contribution and how such achievement was used to determine the final amount of bonus allocated. If the individual contributions were not pre-determined, identify the achievements the Compensation Committee determined and disclose that the goals were not predetermined.

*Response:* In our next annual report or proxy statement, we propose to include the following additional disclosure with respect to our named executive officers' contributions that the Compensation Committee considered with respect to its compensation decisions:

*February 2007 Compensation Determinations*

In the case of Alan J. Main, Ph.D., who was promoted in February 2007 from senior vice president to executive vice president of pharmaceutical research, the compensation committee took into account his contributions toward the achievement of regulatory filings for LX6171 and LX1031, the selection of two additional drug candidates, LX2931 and LX1032, and progress in additional drug discovery programs. In the case of Jeffrey L. Wade, J.D., our executive vice president and general counsel, the compensation committee took into account his contributions toward the completion of a common stock financing and business development and alliance management activities. In the case of Brian P. Zambrowicz, Ph.D., who was named chief scientific officer in February 2007 after serving in 2006 as executive vice president of research, the compensation committee took into account his contributions toward the achievement of regulatory filings for LX6171 and LX1031, the selection of two additional drug candidates, LX2931 and LX1032, and progress in additional drug discovery programs.

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#### *February 2008 Compensation Determinations*

In the case of Dr. Main, the compensation committee took into account his contributions toward the achievement of regulatory filings for LX2931 and LX1032, the selection of an additional drug candidate, LX4211, and progress in additional drug discovery programs. In the case of Mr. Wade, the compensation committee took into account his contributions toward the completion of the Invus and Symphony financings. In the case of Dr. Zambrowicz, the compensation committee took into account his contributions toward the achievement of regulatory filings for LX2931 and LX1032, the selection of an additional drug candidate, LX4211, and progress in additional drug discovery programs. In the case of James F. Tessmer, our vice president of finance and accounting, the compensation committee took into account his management of accounting and finance functions and his operational leadership.

#### *February 2009 Compensation Determinations*

In the case of Dr. Main, the compensation committee took into account his contributions toward the achievement of an investigational new drug application for LX4211, the selection of an additional drug candidate, LX7101, and progress in additional drug discovery programs, as well as his strategic and operational leadership. In the case of Mr. Wade, the compensation committee took into account his contributions in overseeing financial and legal matters and business development activities, as well as his strategic and operational leadership. In the case of Dr. Zambrowicz, the compensation committee took into account his contributions toward the achievement of an investigational new drug application for LX4211, the selection of an additional drug candidate, LX7101, and progress in additional drug discovery programs, as well as his strategic and operational leadership and participation in business development activities. In the case of Mr. Tessmer, the compensation committee took into account his assumption of responsibility as our principal financial and accounting officer and his operational leadership.

#### *February 2010 Compensation Determinations*

In the case of Dr. Main, the compensation committee took into account his contributions toward activities supporting the advancement of our drug candidates in clinical development and progress in our drug discovery programs, as well as his strategic and operational leadership. In the case of Mr. Wade, the compensation committee took into account his contributions toward the completion of a common stock financing and business development and alliance management activities, as well as his strategic and operational leadership. In the case of Dr. Zambrowicz, the compensation committee took into account his contributions toward the advancement of our drug candidates in clinical development with favorable results and progress in our drug discovery programs, as well as his strategic and operational leadership and participation in business development activities. In the case of Mr. Tessmer, the compensation committee took into account his management of accounting and finance functions and his operational leadership.

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The proposed additional disclosure set forth above supplements the proposed disclosure we previously submitted in response to your comment 1 on February 10, 2010. We would note that such previously proposed disclosure references that the Compensation Committee's determinations for Arthur T. Sands, M.D., Ph.D., our president and chief executive officer, were based entirely upon its determination of achievement of the year's corporate goals.

Please do not hesitate to contact the undersigned at (281) 863-3321 with any comments or questions concerning this letter or the above-referenced filings.

Very truly yours,

/s/ Jeffrey L. Wade

Jeffrey L. Wade  
*Executive Vice President and  
General Counsel*