

[LEXICON PHARMACEUTICALS, INC. LETTERHEAD]

February 8, 2011

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

Attention: Ms. Laura Crotty

Re: Lexicon Pharmaceuticals, Inc.
Registration Statement on Form S-3
Filed January 28, 2011
File No. 333-171953

Dear Ms. Crotty:

On behalf of Lexicon Pharmaceuticals, Inc., we submit the following responses to the comments received on February 8, 2011 from the Securities and Exchange Commission's staff with respect to Lexicon's registration statement on Form S-3 (File No. 333-171953). Your comments and our responses to those comments are set forth below.

General

1. It does not appear that you are eligible to conduct a primary offering on Form S-3 under General Instruction I.B.1 to Form S-3 based on your public float. If you disagree, please provide us with a detailed analysis supporting your conclusion. Alternatively, if you are eligible to conduct a primary offering on Form S-3 under General Instruction I.B.6, please provide the information required pursuant to Instruction 7 to General Instruction I.B.6 on the cover page of the filing. Otherwise, please amend your registration statement to revise the form type to a form on which you are eligible to conduct a primary offering.

Response: Please see the detailed analysis attached hereto as Exhibit A supporting our conclusion that the aggregate market value of our voting and non-voting common equity held by non-affiliates was approximately \$247.9 million as of January 27, 2011.

2. Please amend your filing to incorporate by reference each of the two Form 8-Ks filed by the company on March 16, 2010.

Response: We note that both our current reports on Form 8-K dated March 15, 2010 are currently incorporated by reference.

Please do not hesitate to contact the undersigned at (281) 863-3443 with any comments or questions concerning this letter or the above-referenced registration statement.

Very truly yours,

/s/ Brian T. Crum

Brian T. Crum
Vice President and General Counsel

Exhibit A

The following table presents information regarding the aggregate market value of our voting and non-voting common equity held by non-affiliates as of January 27, 2011, as calculated based on the beneficial ownership of our common stock by our directors, executive officers and beneficial owners of ten percent or more of our common stock.

	Number of Shares Beneficially Owned
Invus, L.P., Invus Public Equities, L.P., Invus C.V. and related parties	165,110,497
FMR LLC and related parties	34,235,679
Arthur T. Sands, M.D., Ph.D.	1,635,016
Jeffrey L. Wade, J.D.	34,562
Alan J. Main, Ph.D.	31,562
Brian P. Zambrowicz, Ph.D.	140,489
Steven A. Tragash	—
James F. Tessmer	18,679
Samuel L. Barker, Ph.D.	66,000
Philippe J. Amouyal	—
Raymond Debbane ⁽¹⁾	—
Robert J. Lefkowitz, M.D.	—
Alan S. Nies, M.D.	5,000
Frank P. Palantoni	—
Christopher J. Sobecki	1,000
Judith L. Swain, M.D.	—
Total Shares Held by Affiliates	201,278,484
Total Shares Outstanding	337,474,911
Total Shares Held by Non-Affiliates	136,196,427
Per Share Closing Price	\$ 1.82
Public Float	\$ 247,877,497

(1) Not including 165,110,497 shares held by Invus, L.P., Invus Public Equities, L.P., Invus C.V. and related parties for which Mr. Debbane also reports beneficial ownership.