

[LEXICON PHARMACEUTICALS, INC. LETTERHEAD]

June 7, 2011

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

Attention: Mr. Bryan Pitko

Re: Lexicon Pharmaceuticals, Inc.  
Post-Effective Amendment No. 1 to Form S-3 on Form S-1  
Filed May 26, 2011  
File No. 333-171953

Dear Mr. Pitko:

On behalf of Lexicon Pharmaceuticals, Inc., we submit the following responses to the comments received on June 2, 2011 from the Securities and Exchange Commission's staff with respect to Lexicon's Post-Effective Amendment No. 1 to Form S-3 on Form S-1 (File No. 333-171953). Your comments and our responses to those comments are set forth below.

1. The legal opinion filed as Exhibit 5.1 to your registration statement improperly assumes that at the time of any offering or sale of common stock, the Company will have a sufficient number of authorized shares. Please amend your registration statement to include a revised legal opinion that avoids assumption of material facts underlying the opinion.

*Response:* We confirm that, prior to effectiveness of the registration statement, we will amend the registration statement to include a revised legal opinion in the form attached hereto as Exhibit A which avoids assumption of material facts underlying the opinion.

2. Please confirm that the amount or volume of securities to be sold in the offering and specific information relating to the underwriters and plan of distribution will be disclosed prior to effectiveness of the registration statement.

*Response:* We confirm that the amount or volume of securities to be sold in the offering and specific information relating to the underwriters and plan of distribution will be disclosed prior to effectiveness of the registration statement.

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**

**Exhibit 5.1**

[Letterhead of Vinson & Elkins L.L.P.]

\_\_\_\_\_, 2011

Lexicon Pharmaceuticals, Inc.  
8800 Technology Forest Place  
The Woodlands, Texas 77381

Re: Amendment to Registration Statement on Form S-3 on Form S-1 of Lexicon Pharmaceuticals, Inc.

Ladies and Gentlemen:

We have acted as counsel to Lexicon Pharmaceuticals, Inc. (the "Company"), a Delaware corporation, with respect to certain legal matters in connection with the Company's amendment to its Registration Statement on Form S-3 on Form S-1 (Registration No. 333-171953) (the "Registration Statement") filed by the Company with the Securities and Exchange Commission (the "Commission") under the Securities Act of 1933, as amended (the "Securities Act"), relating to the registration of shares of common stock, par value \$0.001 per share, of the Company (the "Common Stock"). The Common Stock will be offered in amounts, at prices and on terms to be determined in light of market conditions at the time of sale and to be set forth in supplements (each a "Prospectus Supplement") to the Prospectus contained in the Registration Statement

We have examined originals or copies, certified or otherwise identified to our satisfaction, of (i) the Restated Certificate of Incorporation, as amended to the date hereof, and the Amended and Restated Bylaws of the Company, (ii) the Registration Statement, (iii) resolutions of the board of directors of the Company and (iv) such other certificates, statutes and other instruments and documents as we considered appropriate for purposes of the opinions hereafter expressed. In addition, we reviewed such questions of law, as we considered appropriate.

Based on the foregoing, and subject to the assumptions, qualifications, limitations, and exceptions set forth herein, we are of the opinion that, with respect to shares of Common Stock, when (i) the board of directors of the Company has taken all necessary corporate action to approve the issuance and terms of the offering thereof and related matters; and (ii) certificates representing the shares of Common Stock have been duly executed, countersigned, registered and delivered in accordance with the applicable definitive purchase, underwriting or similar agreement approved by the board of directors of the Company, then upon payment of the consideration therefor (not less than the par value of the Common Stock) provided for therein, such shares of Common Stock will be validly issued, fully paid and non-assessable.

The foregoing opinion is limited to the laws of the State of New York, the State of Texas, the General Corporation Laws of the State of Delaware (including the applicable provisions of the Delaware Constitution and the reported judicial decisions interpreting these laws) and the federal laws of the United States of America and we are expressing no opinion as to the effect of the laws of any other jurisdiction, domestic or foreign.

We hereby consent to the filing of this opinion as an exhibit to the Registration Statement and to the use of our name in the Prospectus forming a part of the Registration Statement under the caption "Legal Matters." In giving this consent, we do not admit that we are within the category of persons whose consent is required under Section 7 of the Securities Act and the rules and regulations thereunder.

Very truly yours,