

[LEXICON PHARMACEUTICALS, INC. LETTERHEAD]

August 23, 2011

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

Attention: Ms. Karen Ubell

Re: Lexicon Pharmaceuticals, Inc.
Post-Effective Amendment No. 2 to Form S-3 on Form S-1
Filed August 12, 2011
File No. 333-171953

Dear Ms. Ubell:

On behalf of Lexicon Pharmaceuticals, Inc., we submit the following responses to the comments received on August 17, 2011 from the Securities and Exchange Commission's staff with respect to Lexicon's Post-Effective Amendment No. 2 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. Please disclose prior to effectiveness the amount of securities to be sold in the rights offering and the number of shares each subscription right will be entitled to purchase.

Response: We confirm that the amount of securities to be sold in the rights offering and the number of shares each subscription right will be entitled to purchase will be disclosed prior to effectiveness of the registration statement.

2. The legal opinion of Vinson & Elkins L.L.P. filed as Exhibit 5.1 to your registration statement improperly assumes that at the time of any offering or sale of the Rights Shares, the Company will have a sufficient number of authorized shares available for issuance. 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.

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

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"), related to the issuance by the Company to its stockholders of non-transferable subscription rights (the "Subscription Rights") entitling the holders thereof to purchase shares (the "Rights Shares") of common stock, par value \$0.001 per share (the "Common Stock") of the Company (the "Subscription Rights Offering"). The Registration Statement includes a prospectus (the "Prospectus") to be furnished to stockholders of the Company in connection with the Subscription Rights Offering and relates to the Subscription Rights and the Rights Shares that may be issued and sold by the Company upon exercise of the Subscription Rights. The Subscription Rights and the Rights Shares are collectively referred to herein as the "Securities."

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.

In connection with rendering the opinions set forth below, we have assumed that (i) all information contained in all documents reviewed by us is true and correct, (ii) all signatures on all documents examined by us are genuine and provided by natural persons with legal capacity and authority execute such documents, (iii) all documents submitted to us as originals are authentic and all documents submitted to us as copies conform to the originals of those documents, (iv) the Registration Statement, and any amendments thereto (including post-effective amendments), will have become effective, (v) a Prospectus Supplement will have been prepared and filed with the Commission describing the Securities offered thereby, and (vi) all Securities will be issued and sold in compliance with applicable federal and state securities laws and in the manner specified in the Registration Statement and the applicable Prospectus Supplement.

Based upon and subject to the foregoing, we are of the opinion that:

1. With respect to the Subscription Rights, when (i) the Company has taken all necessary action to approve the issuance and terms of such Subscription Rights, the terms of the Subscription Rights Offering and related matters and (ii) the Subscription Rights have been issued and delivered in accordance with the terms of the Subscription Rights Offering, then the Subscription Rights will constitute valid and legally binding obligations of the Company, in accordance with their terms, except as such enforcement may be subject to any applicable bankruptcy, insolvency, reorganization, fraudulent conveyance or other law relating to or affecting creditors' rights generally and general principles of equity.
2. With respect to the Rights Shares, when (i) the Company has taken all necessary action to approve the issuance of such Right Shares in accordance with the terms of the Subscription Rights Offering and (ii) the Rights Shares have been issued and delivered in accordance with the terms of the Subscription Rights Offering upon payment of the consideration thereof or provided for in the applicable Prospectus Supplement, then the Rights Shares 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.

This opinion letter has been prepared for use in connection with the filing by the Company of the Registration Statement. We assume no obligation to advise you of any changes in the foregoing subsequent to the delivery of this letter.

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,