

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549**

FORM S-3

**REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933**

Lexicon Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of incorporation or organization)

76-0474169
(I.R.S. Employer Identification Number)

**8800 Technology Forest Place
The Woodlands, Texas 77381-1160
(281) 863-3000**

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

**Arthur T. Sands, M.D., Ph.D.
President and Chief Executive Officer
8800 Technology Forest Place
The Woodlands, Texas 77381-1160
(281) 863-3000**

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

**David P. Oelman
Vinson & Elkins L.L.P.
2300 First City Tower
1001 Fannin
Houston, Texas 77002-6760
(713) 758-3708**

**Jeffrey L. Wade
Executive Vice President and General Counsel
Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Place
The Woodlands, Texas 77381-1160
(281) 863-3000**

Approximate date of commencement of proposed sale to the public:

From time to time after this registration statement becomes effective, subject to market conditions and other factors.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. Registration No. 333-161696

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company

(Do not check if a smaller reporting company)

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered (1)	Proposed Maximum Aggregate Offering Price Per Unit	Proposed Maximum Aggregate Offering Price (2)	Amount of Registration Fee
Common Stock, par value \$0.001				N/A
Total	\$18,500,000	\$1.15	\$18,500,000	\$1,319.05(3)

- (1) Includes common stock issuable upon exercise of the underwriters' over-allotment option.
- (2) This registration statement relates to the registrant's registration statement on Form S-3 (Registration No. 333-161696) (the "Prior Registration Statement"). In accordance with Rule 462(b) under the Securities Act of 1933, as amended, an additional amount of securities having a proposed maximum aggregate offering price of no more than 20% of the proposed maximum aggregate offering price of the remaining securities eligible to be sold under the Prior Registration Statement (\$92,500,002), or \$18,500,000, may be registered hereby.
- (3) Calculated pursuant to Rule 457(o) under the Securities Act. As the \$12,514 previously paid with respect to unsold securities registered on Form S-3 (Registration No. 333-122214) filed by the registrant on January 21, 2005 exceeds both the amount of registration fee due for the securities registered on Form S-3 (Registration No. 333-161696) and the amount of registration fee due hereunder, no fee is being paid herewith pursuant to Rule 457(p) under the Securities Act of 1933, as amended.

This registration statement shall become effective upon filing with the Securities and Exchange Commission in accordance with Rule 462(b) under the Securities Act of 1933, as amended.

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EXPLANATORY NOTE

This registration statement is being filed with respect to the registration of an additional \$18,500,000 of shares of common stock, par value \$0.001 per share, of Lexicon Pharmaceuticals, Inc., a Delaware corporation, pursuant to Rule 462(b) under the Securities Act of 1933, as amended, and General Instruction IV of Form S-3 promulgated thereunder. This registration statement relates to the registrant's shelf registration statement on Form S-3 (Registration No. 333-161696) (the "Prior Registration Statement"), initially filed by the registrant on September 2, 2009, and declared effective by the Securities and Exchange Commission on September 18, 2009. The required opinion and consent of counsel and consent of independent auditor are attached hereto and filed herewith. Pursuant to Rule 462(b), the contents of the Prior Registration Statement, including the exhibits thereto, are incorporated by reference into this registration statement.

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 16. Exhibits.

<u>Exhibit No.</u>	<u>Description</u>
5.1	— Opinion of Vinson & Elkins L.L.P.
23.1	— Consent of Independent Registered Public Accounting Firm.
23.2	— Consent of Vinson & Elkins L.L.P. (contained in Exhibit 5.1).
24.1*	— Power of Attorney.

* Incorporated by reference to the signature page to the registrant's registration statement on Form S-3 (Registration No. 333-161696).

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of The Woodlands, in the State of Texas, on March 15, 2010.

Lexicon Pharmaceuticals, Inc.

By: /s/ ARTHUR T. SANDS
Arthur T. Sands, M.D., Ph.D.
President and Chief Executive Officer

Pursuant to the requirements of the Securities Act of 1933, as amended, this registration statement has been signed below by the following persons in the capacities and on the dates indicated below.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
* Arthur T. Sands, M.D., Ph.D.	President, Chief Executive Officer and Director (principal executive officer)	March 15, 2010
* James F. Tessmer	Vice President, Finance and Accounting (principal financial officer and principal accounting officer)	March 15, 2010
* Samuel L. Barker, Ph.D.	Chairman of the Board of Directors	March 15, 2010
* Philippe J. Amouyal	Director	March 15, 2010
* Raymond Debbane	Director	March 15, 2010
* Robert J. Lefkowitz, M.D.	Director	March 15, 2010
* Alan S. Nies, M.D.	Director	March 15, 2010
* Frank Palantoni	Director	March 15, 2010
* Christopher J. Sobecki	Director	March 15, 2010
* Judith L. Swain, M.D.	Director	March 15, 2010

*By: /s/ JEFFREY L. WADE
Name: Jeffrey L. Wade
Title: Attorney-In-Fact

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24.1*	— Power of Attorney.

* Incorporated by reference to the signature page to the registrant's registration statement on Form S-3 (Registration No. 333-161696).

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

March 15, 2010

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

Re: Registration Statement on Form S-3 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 Registration Statement on Form S-3 (the "Registration Statement") filed pursuant to Rule 462(b) under the Securities Act of 1933, as amended (the "Securities Act"), relating to the registration by the Company under the Securities Act of an additional \$18,500,000 of shares (the "Additional Shares") of the Company's common stock, par value \$0.001 per share (the "Common Stock"). The Registration Statement incorporates by reference the Registration Statement on Form S-3 (Registration No. 333-161696) (the "Prior Registration Statement"), which was declared effective by the Securities and Exchange Commission (the "Commission") on September 18, 2009.

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) the Prior Registration Statement, (iv) resolutions of the board of directors of the Company and (v) such other certificates, statutes and other instruments and documents as we considered appropriate for purposes of the opinion 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 will have become effective pursuant to Rule 462(b) promulgated under the Securities Act, (v) a supplement (a "Prospectus Supplement") to the prospectus contained in the Prior Registration Statement will have been prepared and filed with the Commission describing the Additional Shares offered thereby, (vi) all Additional Shares will be

issued and sold in compliance with applicable federal and state securities laws and in the manner specified in the Prior Registration Statement and the applicable Prospectus Supplement, (vii) at the time of any offering or sale of the Additional Shares, that the Company shall have such number of shares of Common Stock authorized or created and available for issuance and (viii) a definitive purchase, underwriting or similar agreement with respect to the Additional Shares offered will have been duly authorized and validly executed and delivered by the Company and the other parties thereto.

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 the Additional Shares, 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 Additional Shares 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 duly authorized, 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,

/s/ Vinson & Elkins L.L.P.

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the reference to our firm under the caption "Experts" in this Registration Statement (Form S-3) of Lexicon Pharmaceuticals, Inc. for the registration of an additional \$18,500,000 of shares of its common stock and to the incorporation by reference therein of our reports dated March 5, 2010 with respect to the consolidated financial statements of Lexicon Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Lexicon Pharmaceuticals, Inc., included in its Annual Report (Form 10-K) for the year ended December 31, 2009 filed with the Securities and Exchange Commission.

/s/ ERNST & YOUNG LLP

Houston, Texas
March 16, 2010