[LEXICON PHARMACEUTICALS, INC. LETTERHEAD]

December 23, 2009

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

Attention: Ms. Nandini Acharya

Re: Lexicon Pharmaceuticals, Inc.
Form 10-K for the year ended December 31, 2008
Filed March 6, 2009
File No. 000-30111

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

Dear Ms. Acharya:

On behalf of Lexicon Pharmaceuticals, Inc., we submit the following responses to the comments received on November 30, 2009 from the Securities and Exchange Commission's staff with respect to Lexicon's annual report on Form 10-K for the year ended December 31, 2008 and definitive proxy statement for Lexicon's 2009 annual meeting. Your comments and our responses to those comments are set forth below.

Form 10-K

Item 1. Business
Drug Discovery and Development Collaborations, page 5

1. With respect to each drug discovery and collaboration agreement referenced in this section, please disclose the upfront payments and research funding received to date, the aggregate potential milestone payments and the potential range of royalty payments (for example, "low-teens" or "high-teens"). We note that you have included some information regarding the upfront payments and research funding amounts with respect to these agreements in the notes to the financial statements but this is material information which should be consolidated in the Business section.

Response: In future filings beginning in the Form 10-K for the year ended December 31, 2010, we propose to disclose in the Business section under the subheading "Drug Discovery and Development Collaborations" the following information regarding upfront payments and research funding received to date and aggregate potential milestone payments:

> *Bristol-Myers Squibb Corporation*. We have received $86 million in upfront payments and research funding under the agreement. In addition, we are entitled to receive clinical and regulatory milestone payments ranging, depending on the timing and extent of our efforts in the alliance, up to $76 million for each drug developed by Bristol-Myers Squibb under the alliance. We will also earn royalties on sales of drugs commercialized by Bristol-Myers Squibb under the alliance.

Genentech, Inc. We have received $58 million in upfront payments, research funding and research milestone payments under the agreement. In addition, we are entitled to receive clinical and regulatory milestone payments ranging, depending on the extent of our efforts in the alliance, up to $25 million for each drug target for which Genentech develops a biotherapeutic drug under the alliance. We will also earn royalties on sales of biotherapeutic drugs commercialized by Genentech under the alliance.

N.V. Organon. We have received $52.5 million in upfront payments and research funding under the agreement.

Takeda Pharmaceutical Company Limited. We have received $18.5 million in upfront payments and research milestone payments under the agreement. In addition, we are entitled to receive clinical development and product launch milestone payments of up to $29 million for each drug developed by Takeda under the alliance. We will also earn royalties on sales of drugs commercialized by Takeda under the alliance.

We believe that the potential ranges of royalty payments under each of these agreements are not material to investors due to the uncertain and remote nature of any such payments. Each of the drug discovery and development programs being pursued under each of these alliances remain in early-stage research, with none having yet entered human clinical trials and no assurance of ever reaching that stage. Even after a drug candidate enters clinical development, human clinical trials are inherently risky and time-consuming, with a high degree of uncertainty as to the safety and efficacy of a potential drug product and the ultimate approval of such drug product by regulatory authorities. As a result, any royalties payable under these agreements are highly uncertain in nature and will only occur, if at all, many years in the future.

In this regard, we also note that we are engaged in drug discovery and development programs outside of these alliances that are at a substantially more advanced stage of development, with four drug candidates presently in Phase 2 clinical development and other drug candidates in preclinical development in preparation for making regulatory filings to permit the initiation of human clinical trials.

Finally, consistent with our requests for confidential treatment of royalty rate information in each of the agreements in question (all of which requests have been granted by the staff), we believe that any value to investors from the disclosure of potential ranges of royalty payments is significantly outweighed by the competitive disadvantage we and our collaborators would suffer as a result. Among other things, the disclosure of potential ranges of royalty payments would place us at a disadvantage in negotiating with potential future collaborators and could negatively affect our relationships and good will with existing collaborators.

At your request, we are submitting the royalty rates applicable to each of these agreements under separate cover pursuant to Rule 83 under the Freedom of Information Act.

Patents and Proprietary Rights, page 9

2. Please revise your disclosure to include a discussion of all material patents or groups of patents and indicate whether such patents are held directly by you or licensed from a third party. For each material patent, the disclosure should include a discussion of the technologies that relate to such patent, the jurisdiction in which the patent is granted and the expiration date.

Response: In future filings beginning in the Form 10-K for the year ended December 31, 2010, we propose to disclose in the Business section under the subheading "Patents and Proprietary Rights" the following information regarding presently issued and pending patents relating to our development-stage drug candidates:

> We own patent applications, and in some cases issued patents, covering each of our drug candidates in clinical and preclinical development, including:
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> § patent applications pending worldwide that claim LX1031 and associated crystalline forms, pharmaceutical compositions, and methods of manufacture and use, which we have exclusively licensed to Symphony Icon pursuant to our product development collaboration with Symphony Icon.
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> § patent applications pending worldwide that claim LX1032 and associated crystalline forms, pharmaceutical compositions, and methods of manufacture and use, from which one U.S. patent has issued to date, which we have exclusively licensed to Symphony Icon pursuant to our product development collaboration with Symphony Icon.
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> § patent applications pending worldwide that claim LX2931 and associated crystalline forms, pharmaceutical compositions, and methods of manufacture and use, from which one U.S. patent has issued to date.
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> § patent applications pending worldwide that claim LX4211 and associated crystalline forms, pharmaceutical compositions, and methods of manufacture and use.
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> § patent applications pending worldwide that claim LX7101 and associated pharmaceutical compositions, and methods of manufacture and use.
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> Patents extend for varying periods according to the date of patent filing or grant and the legal term of patents in the various countries where patent protection is obtained. The actual protection afforded by a patent, which can vary from country to country, depends on the type of patent, the scope of its coverage and the availability of legal remedies in the country. We have filed patent applications and, in some cases, hold issued patents covering each of our drug candidates in clinical and preclinical development. While the patents issued under such applications have or will have a variety of expiration dates, depending on, among other things, the date of filing and possible patent term extension, no U.S. patent that has issued or may issue based on a patent application we have filed relating to one of our drug candidates in clinical or preclinical development has a normal expiration date earlier than 2026.

3. We note that you license your principal gene targeting technologies from GenPharm International, Inc. We further note the disclosure on page 28 of your filing indicating that there is a dispute with the University of Utah Research Foundation regarding your payment of royalties under this agreement. Please revise your disclosure to include the material terms of the licensing agreement with GenPharm International, Inc. and file the agreement as an exhibit or provide us with an analysis setting forth your determination that this agreement is not material to your business.

Response: We determined that our license agreement with GenPharm is not material to our business based on, among other considerations, the facts that (a) we have alternative technologies that enable the generation of knockout mice (e.g., our proprietary gene trapping technologies) that do not require use of the patented technology and (b) our financial obligations under the agreement are not material. The gene targeting technologies licensed from GenPharm have minimal application relative to our current drug discovery activities, and no implications for any of our drug candidates in clinical or preclinical development. We are no longer using the technologies that originated with the University of Utah Research Foundation and were the subject of the referenced dispute. The dispute itself was settled in September 2009.

DEF 14A

Executive and Director Compensation
Compensation Discussion and Analysis, page 24

4. We note your disclosure that payment of cash bonuses is determined by taking into account both pre-determined corporate and individual goals. While you have disclosed the corporate goals, whether or not those goals were achieved and how the achievement was tied to the level of bonus paid, you have not provided similar disclosure with respect to individual goals. Accordingly, please provide us with sample disclosure for inclusion in your next annual report or proxy statement which sets forth the individual goals for each executive officer, whether such goals were achieved and how the achievement of such goals was tied to the amount of bonus paid.

Response: In our next annual report or proxy statement, we propose to include the following additional disclosure with respect to individual goals:

> For executive officers other than Dr. Sands, our president and chief executive officer, the compensation committee also took into account individual goals, which consisted principally of the expected individual contributions of each executive officer towards the achievement of the year's corporate goals, together with Dr. Sands' and the committee's independent assessment of each executive officer's overall performance and contributions to the company during the year. Dr. Sands had no individual goals in [2009] apart from the corporate goals.
>
> The committee's determinations for Dr. Sands were based entirely upon its determination of achievement of the year's corporate goals. For other executive officers, the compensation committee based its determinations principally upon its determination of achievement of the year's corporate goals, but also took into account, to a lesser extent, each executive officer's individual contributions towards the achievement of such corporate goals, together with Dr. Sands' and the committee's independent assessment of each executive officer's overall performance and contributions to the company during the year.

As requested by the staff, we are providing the following acknowledgements:

- we are responsible for the adequacy and accuracy of the disclosure in the foregoing filings;
- staff comments or changes to disclosure in response to staff comments do not foreclose the Commission from taking any action with respect to such filings; and
- we may not assert staff comments as a defense in any proceeding initiated by the Commission or any person under federal securities laws of the United States.

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