

[Lexicon Pharmaceuticals, Inc. Letterhead]

February 8, 2008

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

Attention: Mr. Mark Brunhofer
Division of Corporate Finance

Re: Lexicon Pharmaceuticals, Inc.
Form 10-K for the fiscal year ended December 31, 2006
Form 10-Q for the quarterly period ended September 30, 2007
File No. 000-30111

Dear Mr. Brunhofer:

On behalf of Lexicon Pharmaceuticals, Inc., we have set forth our responses to the comments received from Securities and Exchange Commission's staff in its January 25, 2008 letter regarding our annual report on Form 10-K for the fiscal year ended December 31, 2006 and our quarterly report on Form 10-Q for the quarterly period ended September 30, 2007. For your convenience, we have listed our responses in the same order as the comments were presented and have repeated each comment prior to the response.

Form 10-K for the Fiscal Year Ended December 31, 2006

Notes to Consolidated Financial Statements

Note 2: Summary of Significant Accounting Policies
Revenue Recognition, page F-8

1. In your response to our previous comment one you indicate that you do not consider your collaborator's option to extend the initial research period in determining the service period over which you amortize your upfront fees because you have historical evidence that indicates that some collaborators have exercised their option while others have not. However, your response and revenue recognition disclosure is unclear on how you treat the unamortized portion of your deferred upfront fees when it becomes probable that your collaborator will exercise its option to extend the research period. Please revise the proposed disclosure to clarify how you account for the upfront fee when it becomes probable that your collaborator will extend the research period. In this regard, if you do not amortize the remaining deferred upfront fees over the remaining service period including the period of extension, please explain to us how your accounting complies with GAAP by referencing the authoritative literature you rely upon to support your accounting.

Response: We have had only one occurrence in which it became probable that a collaborator would exercise its option to extend the research period, which was with respect to our arrangement with Bristol-Myers Squibb Company ("BMS"). In May 2006, BMS extended the target discovery term of the alliance for an additional two years in exchange for \$20.0 million in additional research funding over the two year extension, which commenced in January 2007.

When collaborator agreements are negotiated, the terms relating to the initial research period and any extension research periods are all negotiated simultaneously and are negotiated based on the expected level of effort that would be required under each portion of the agreement. In the case of BMS, the level of work associated with the extensions did vary and the amount of fees was negotiated to be reflective of the level of work required during each of the optional extension alternatives, as more fully described below. However, at the onset of the alliance, neither of the extension alternatives were included in the determination of the amortization period for revenue recognition, as it was unknown as to whether or not BMS would exercise either extension alternative.

When it became probable that BMS was going to extend the research period, we reassessed the level of effort expected to be required to perform our obligations with respect to the extended research period. We determined there were no significant changes in the expected level of work from the initial negotiation of the agreement.

During the initial research period, we agreed to complete the development and Level 1 phenotypic analysis of 4,000 lines of mutant mice and Level 2 phenotypic analysis for the first 3,000 lines of mutant mice for which Level 1 phenotypic analysis was completed that displayed potential utility of the corresponding gene in the neuroscience field. During the initial research period, we were required to provide at least 100 employees working on a dedicated full time basis ("FTEs", as defined by the agreement) per year. Our obligations with respect to this initial research period of three years were in exchange for an upfront payment of \$36.0 million and research funding of \$30.0 million to be paid in quarterly increments over the initial research period, or \$66.0 million in total. At the end of the initial research period, BMS had two options to extend the research period:

- (A) In exchange for \$20.0 million, to be paid in quarterly increments over two years, we would complete Level 2 phenotypic analysis for an additional 1,000 lines of mutant mice for which Level 1 phenotypic analysis was completed that displayed potential utility of the corresponding gene in the neuroscience field. Under this option, we would be required to provide at least 40 FTEs per year during the two-year extension period.

(B) In exchange for \$50.0 million, to be paid in quarterly increments over two years, we would complete Level 1 phenotypic analysis for an additional 1,000 lines of mutant mice and Level 2 phenotypic analysis for an additional 2,000 lines of mutant mice for which Level 1 phenotypic analysis was completed that displayed potential utility of the corresponding gene in the neuroscience field. Under this option, we would be required to provide at least 100 FTEs per year during the two-year extension period.

If neither option were exercised by BMS and the research period ended after three years, the total funding would have been \$66.0 million for a minimum of 100 FTEs per year, or \$22.0 million per year. This equates to \$220,000 per FTE per annum. Under Option A (which BMS selected), the additional \$20.0 million of funding for 40 FTEs per year equates to \$250,000 per FTE. Under Option B, the additional \$50.0 million of funding for 100 FTEs per year also equates to \$250,000 per FTE. As there was a significant upfront payment of cash, we believed it was financially reasonable to have a slight discount on an FTE basis for payments due with respect to the initial research period based on the time value of money.

Since the level of effort with regard to the extended research period was different than the level of effort required during the initial research period, we believe the revenue recognized with respect to work performed pursuant to such periods should also reflect a similar pattern. We were not able to identify any authoritative literature directly applicable to our specific situation, but we did consider proportional performance methods used in service industries as described in SAB 104, which allows the change in the level of services provided to a customer to be reflected in the revenue recognition pattern. Since the intent of the original terms of the agreement was that the fees be consistent in relation to the level of effort required with respect to each period of the agreement, as noted above, we believe we applied appropriate judgment in recognizing the remainder of the upfront fees over the original research period and the fees associated with the extended research period over the term of the two-year extension period. We believe the revenue recognition methodology that we have applied is consistent with the recognition of revenue using an outputs-based proportional performance approach.

In future filings beginning in the Form 10-K for the year ended December 31, 2007, we propose to disclose in a footnote to our financial statements the following statement, with the additional passages that were not included in the Form 10-K for the year ended December 31, 2006 underlined:

Upfront fees under drug discovery alliances are recognized as revenue on a straight-line basis over the estimated period of service, generally the contractual research term, as this period is Lexicon's best estimate of the period over which the services will be rendered, to the extent they are non-refundable. Lexicon has determined that the level of effort it performs to meet its obligations is fairly constant throughout the estimated periods of service. As a result, Lexicon has determined that it is appropriate to recognize revenue from such agreements on a straight-line basis, as management believes this reflects how the research is provided during the initial period of the agreement. When it becomes probable that a collaborator will extend the research period, Lexicon adjusts the revenue recognition method as necessary based on the level of effort required under the agreement for the extension period.

Form 10-Q for the Quarterly Period Ended September 30, 2007

Notes to Consolidated Financial Statements

Note 7: Arrangements with Symphony Icon, Inc., page 9

2. We acknowledge your response to our previous comment 3a. You indicate that you believe your option to purchase Symphony Icon from Holdings is a variable interest in Symphony Icon as defined under paragraph 2c of FIN 46R. Please elaborate for us how this option qualifies as a variable interest under paragraph 2c of FIN 46R. In this regard, please demonstrate for us how this option represents an investment in Symphony Icon and how it is at risk as addressed in paragraphs 5 and B7 of FIN 46R. In addition, please revise your proposed disclosure to identify your variable interest, how it is at risk and, consistent with your response, that you intend to exercise your option if the development of Symphony Icon is successful.

Response: As noted in our previous response, we determined that Symphony Icon is a variable interest entity under paragraphs 5(b)(1) and 5(b)(3) of FIN 46R as Holdings, the equity investor in Symphony Icon, lacks the exclusive ability to make decisions about Symphony Icon's activities that have a significant effect on its success and is limited in its potential returns if we exercise our purchase option. We believe that Holdings is a variable interest holder in Symphony Icon as Holdings owns all outstanding equity in Symphony Icon. We also believe that we are a variable interest holder in Symphony Icon as we have granted to Symphony Icon an exclusive license (even as to Lexicon) to the intellectual property relating to the drug programs and issued shares of our common stock to Holdings in return for an exclusive option from Holdings to purchase all of Symphony Icon's equity at a predetermined price. Symphony Icon's primary asset is the exclusive license to the contributed intellectual property, including any rights resulting from the continued development of the drug programs.

We have applied Ernst & Young LLP's FIN 46R FAQ 5(a)-18, which provides that transactions occurring outside the entity may be considered in determining whether an entity has a variable interest. In our fact pattern, we have been granted an option to buy all of the outstanding equity of Symphony Icon from Holdings at a fixed price. Accordingly, we believe, through application of this interpretive guidance (which also includes excerpts from a speech given by Jane D. Poulin, an SEC staff member, on the topic), we have a variable interest in Symphony Icon. In addition, by limiting Holdings' returns from Symphony Icon, Symphony Icon is a variable interest entity.

After considering these factors, we believe we have appropriately applied the requirements of FIN 46R in determining that Lexicon is a variable interest holder of Symphony Icon.

We further noted in our previous response that we believe that Holdings and Lexicon, the variable interest holders in Symphony Icon, are related parties under paragraph 16(d) of FIN 46R as approval is needed from Lexicon before Holdings could sell, transfer, or encumber its ownership in Symphony Icon. Finally we noted that we were the primary beneficiary principally due to our responsibilities with respect to the activities of Symphony Icon.

In future filings, beginning in the Form 10-K for the year ended December 31, 2007, we propose to disclose in a footnote to our financial statements the following statement:

In accordance with FIN 46R, Lexicon has determined that Symphony Icon is a variable interest entity for which it is the primary beneficiary. This determination was based on Holdings' lack of controlling rights with respect to Symphony Icon's activities and the limitation on the amount of expected residual returns Holdings may expect from Symphony Icon if Lexicon exercises its Purchase Option. Lexicon has determined it is a variable interest holder of Symphony Icon due to its contribution of the intellectual property relating to the Programs and its issuance of shares of its common stock in exchange for the Purchase Option, which Lexicon intends to exercise if the development of the Programs is successful. Lexicon has determined that it is a primary beneficiary as a result of certain factors, including its primary responsibility for the development of the Programs and its contribution of the intellectual property relating to the Programs.

3. We acknowledge your response to our previous comment 3d. Please elaborate on why you analogize to the guidance in paragraph 8a of EITF 00-6 to record the value of your option to purchase Symphony Icon as a charge to minority interests on the balance sheet. In this regard, paragraph 8a appears to apply solely to forward purchase contracts and appears to be superceded by paragraph 20 since the effectiveness of SFAS 150; requiring the contract to be valued at fair value and precluding minority interest accounting going forward. In your response, please explain to us why it is not appropriate to carry your option to purchase Symphony Icon as an asset. To further understand your accounting and given that Symphony Icon has funding in excess of the minority interest carried on your balance sheet as a result of charging the \$8.6 million value of your option to acquire Symphony Icon and your \$2.2 million share of transaction costs to minority interests, please explain to us how you intend to account for:
- any losses of Symphony Icon in excess of the minority interest carried on your balance sheet that have already been funded by Holdings; and
 - any dissolution of Symphony Icon in which funds are returned to Holdings in an amount greater than the minority interests carried on your balance sheet.

Response: After further review of the guidance referenced above and upon further analysis, we believe that it is appropriate to record the value of our option to purchase the outstanding equity of Symphony Icon as an asset instead of a charge to minority interests on our balance sheet. We also believe that the value of the purchase option should be amortized to expense using a straight-line method over the purchase option period. We may elect to exercise the purchase option at any time beginning on the one-year anniversary of the closing date of the Symphony transaction (June 15, 2007) and ending on the four-year anniversary of the closing date. As we do not know when we will elect to exercise this option, if at all, we believe the period over which the purchase option should be amortized should be four years. We intend to assess for potential impairment whenever events or changes in circumstances indicate that the asset's carrying amount may not be recoverable. In addition, if we elect to exercise the purchase option prior to the expiration of the four-year option period, we will impair any remaining balance. We intend to reclassify the purchase option as an asset on our consolidated balance sheet and record the amortization in the consolidated statement of operations in future filings beginning in the Form 10-K for the year ended December 31, 2007.

We considered whether the purchase option should be considered a derivative. The purchase option does not meet the criteria in paragraph 6 of SFAS No. 133 to be designated a derivative and require fair value accounting. Because this instrument is not a derivative in accordance with SFAS 133, we believe fair value accounting is not appropriate. We do believe that the payment for the option is an asset. The amount paid for that asset essentially provides Lexicon a time period in which to exercise its right to purchase all of the equity of Symphony Icon. Accordingly, we are applying one of the choices stated in the AICPA Issues Paper, "Accounting for Options", that provides for amortization of the purchased option. We believe that the straight line method would provide the most systematic method for such amortization.

As we intend to file the Form 10-K for the year ended December 31, 2007 in the near term (March 2008), we prefer to make the change to record the value of the purchase option as an asset instead of a charge to minority interests in our financial statements in that Form 10-K. We propose to record the amortization for the period from the closing date of the Symphony transaction through December 31, 2007 during the quarter ended December 31, 2007 as we have concluded that the amortization that relates to the quarter ended September 30, 2007 of \$535,000 (3.8% and 1.1% of our net loss for the three and nine months ended September, 30, 2007, respectively) is not material to the previously reported financial statements such that an amendment to our Form 10-Q for the quarterly period ended September 30, 2007 would be necessary. Additionally, we do not believe this would significantly impact the quality of our earnings trends.

We intend to account for losses of Symphony Icon by reducing the minority interest carried on our balance sheet until this balance has been reduced to zero, and then we will stop allocating losses to the minority interest, at which time we will absorb all of Symphony Icon's losses. If there were a dissolution of Symphony Icon in which funds were returned to Holdings in an amount greater than the minority interest carried on our balance sheet, the excess of the funds returned to Holdings over the carrying value of the minority interest would be recognized as a reduction in earnings available to our common shareholders, or as a deemed dividend.

Note 8: Agreements with Invus, L.P., page 10

4. In your response to our previous comment 4a you indicate that you intend to revise your disclosure in future filings to clarify the mechanics of the terminations of the warrants associated with your Invus agreement. As previously requested, please provide us the disclosure you intend to include in your future filings.

Response: In future filings beginning in the Form 10-K for the year ended December 31, 2007, we propose to disclose in a footnote to our financial statements the following statement, with the additional passages that were not included in the Form 10-Q for the quarterly period ended September 30, 2007 underlined:

Lexicon entered into a Securities Purchase Agreement (the "Securities Purchase Agreement") with Invus under which the Company issued and sold to Invus 50,824,986 shares in an initial investment (the "Initial Investment") and permitted Invus to require, subject to specific conditions, that the Company conduct certain rights offerings (the "Rights Offerings"). In connection with the Securities Purchase Agreement, Lexicon also entered into a Warrant Agreement with Invus under which the Company issued to Invus warrants (the "Warrants") to purchase 16,498,353 shares of its common stock at an exercise price of \$3.0915 per share. The Warrant Agreement provided that, to the extent not previously exercised, the Warrants would terminate concurrently with the closing of the Initial Investment.

Initial Investment. In the Initial Investment which closed on August 28, 2007, Invus purchased 50,824,986 shares of Lexicon's common stock for a total of approximately \$205.4 million, resulting in net proceeds of \$198.1 million after deducting fees and expenses of approximately \$7.3 million. Simultaneously with the closing of the Initial Investment, all Warrants issued under the Warrant Agreement terminated unexercised according to their terms. This purchase resulted in Invus' ownership of 40% of the post-transaction outstanding shares of Lexicon's common stock.

5. We acknowledge your response to our previous comment 4b. You indicate in your response that you may not have sufficient shares of common stock authorized to settle your potential obligations under the rights offerings if your common stock price were to drop below \$2.37 per share. You also appear to conclude that there would be no net settlement in either cash or shares if your stock price declines below \$2.37 per share because there would be no gain or loss associated with a transaction at the then fair value. Paragraph 19 of EITF 00-19 clearly indicates that if an instrument could cause a company to seek an increase in authorized shares, share settlement is not within the control of the company and asset or liability classification is required. As it does not appear that there is an explicit or implicit limit on the number of shares that could be issued under the rights offerings, please revise your accounting and disclosure to record the fair value of your obligation to conduct rights offerings as a liability and mark the liability to fair value at each reporting date with the changes in value being reflected in your statements of operations. In addition, consistent with the guidance in paragraphs 10 and 11 of EITF 00-19 please explain to us whether the existence of these rights offerings and the potential issuance of shares in excess of those authorized taints any other outstanding options, warrants or similar instruments. Otherwise, please explain to us the mechanics of how future share issuances at a then fair value of less than \$2.37 per share will be capped to avoid exceeding your currently authorized share limit.

Response: We understand the broad intent of EITF 00-19 as requiring liability accounting for any transactions that would possibly require net cash settlement outside of the issuer's control. We believe we have met the intent of EITF 00-19 as there is no scenario under any potential rights offering that will require net cash settlement.

Under the terms of the securities purchase agreement, any rights offering will be transacted, at the option of Invus, at a stock price equal to or greater than the fair value of the common stock on the date of such rights offering if the market price is less than \$4.50 per share at such time. In this scenario, all shareholders who choose to participate in such rights offering by purchasing common stock at a market price would realize no gain or loss on the exercise of such rights. That is, there could be no net cash settled under EITF 00-19 as the value to be net settled would be \$0 if the price selected was the market price. If the price selected was in excess of the market price, the investor would in essence be paying a premium, which we believe is not relevant to the analysis as it is not economically beneficial to the investor to do so.

Conversely, any rights offering will be transacted, at the option of Invus, at a stock price equal to or less than the fair value of the common stock on the date of such rights offering (but no less than \$4.50 per share) if the market price is equal to or greater than \$4.50 per share at such time. In any case, there would be a sufficient number of authorized shares to allow for the rights offering, both on a gross physical basis as well as a net settled basis.

As discussed in paragraph 12 of EITF 00-19, contracts that include any provision that could require net-cash settlement cannot be accounted for as equity of the company. Paragraph 13 of EITF 00-19 further states, "Because any contract provision that could require net-cash settlement precludes accounting for a contract as equity of the company (except for those circumstances in which the holders of the underlying shares would receive cash, as discussed in paragraphs 27 and 28), all of the following conditions must be met for a contract to be classified as equity." That sets the context for the following paragraphs, which include the guidance in paragraph 19. We believe paragraph 19 is not an absolute test within itself, but rather must be considered in light of the overall principle expressed in the guidance in paragraph 13. That is, even if there are not sufficient shares at a certain price (below \$2.37 in Lexicon's case) to gross physically settle the contract, we do not believe that a net cash settlement can be presumed as any such presumption is rebutted by the fact that there would be no net settlement of any kind for that contract as there would be no net gain or loss.

As a result, we believe there are no provisions under the securities purchase agreement that would require net-cash settlement as there is no scenario that would require us to provide any cash in any rights offering. Therefore, we believe is appropriate to classify this contract as an equity transaction. Additionally, we do not believe that the existence of Invus' right to require us to initiate these rights offerings and the potential issuance of shares in excess of those currently authorized taints any other outstanding instruments as the only outstanding instruments are stock options under our incentive and directors' stock option plans and approximately 16,000 warrants.

If you have any further questions or require additional information, please do not hesitate to contact me at (281) 863-3321.

Very truly yours,

/s/ Jeffrey L. Wade

Jeffrey L. Wade
Executive Vice President and
General Counsel