

Via Facsimile and U.S. Mail
Mail Stop 6010

June 1, 2007

Ms. B. Lynne Parshall, J.D.
Chief Financial Officer
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

**Re: Isis Pharmaceuticals, Inc.
Form 10-K for the Fiscal Year Ended December 31, 2006
Filed March 16, 2007
File No. 000-19125**

Dear Ms. Parshall:

We have limited our review of your filings to those issues we have addressed in our comments. In our comments, we ask you to provide us with information so we may better understand your disclosure.

Please understand that the purpose of our review process is to assist you in your compliance with the applicable disclosure requirements and to enhance the overall disclosure in your filing. We look forward to working with you in these respects. We welcome any questions you may have about our comments or on any other aspect of our review. Feel free to call us at the telephone numbers listed at the end of this letter.

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

Management's Discussion and Analysis of Financial Condition and Results of Operations, page 52

Critical Accounting Policies, page 54

1. Your discussion of critical accounting policies does not explain how the estimates have affected your results of operations. Provide to us proposed disclosure that quantifies how accurate your estimates and assumptions have been in the past. Refer to Release No. 33-8350.

2. In addition to the above, please provide us with additional information, in a disclosure-type format, regarding the information that you rely on in estimating your continuing obligations under your agreements with Antisense Therapeutics, Ltd., Lilly, OncoGenex and Pfizer. Specifically, tell us how you estimate your remaining performance obligation under each arrangement and provide us with proposed disclosure for Note 6 that details the following:
 - The amount of the milestone payments or up-front fees received, the amount recognized within revenue for each financial statement period presented, and the related amortization period for any amounts deferred; and
 - Whether or not you have changed your estimate of the remaining performance period under each arrangement and how such a change in estimate impacted your results of operations for the financial statement periods presented.

Notes to Consolidated Financial Statements, page F-7

Note 1. Organization and Significant Accounting Policies, page F-7

3. Based on your disclosure herein and on page 57 of your Management's Discussion and Analysis, it appears that you capitalize inventory costs related to drugs that you utilize in clinical development activities. Please provide us with additional information, in a disclosure-type format, that clarifies why you believe your accounting policy is appropriate. Please address SFAS No. 2 or other literature as applicable.

Note 4. Stockholders' Equity, page F-19

Warrants, page F-26

4. Please provide us with your analysis, in a disclosure-type format, as to whether the warrants issued in your April 2006 Symphony GenIsis Holdings LLC transaction qualify as a derivative instrument within the scope of SFAS No. 133, which would necessitate that you account for those warrants at fair value and record changes in that fair value within earnings. Additionally, please provide us with an analysis under EITF No. 00-19 that supports your classification of these warrants as an equity instrument. The registration rights agreement filed as Exhibit 10.3 to your March 31, 2006 Form 10-Q appears to indicate that you have an obligation to maintain the effectiveness of the related registration statement, as well as other Exchange Act timely reporting obligations. Please refer to paragraphs 14, 18 and 25 of EITF No. 00-19.

5. Please provide us with information that supports your decision to reclassify the warrant liability associated with your August 2005 private placement from liabilities to equity on your statement of financial position for the year ended December 31, 2005. Address in your response whether you have any continuing obligations similar to those in the preceding comment to keep an underlying registration statement effective and make timely Exchange Act filings.
6. Please tell us how you viewed and accounted for the registration rights agreement related to both your December 31, 2005 private placement transaction and the Symphony GenIsis transaction in relation to EITF No. 05-4. Refer to the Division of Corporation Finance "Current Accounting and Disclosure Issues" Section II (B) - Classification and Measurement of Warrants and Embedded Conversion Features (New). You can find this at the following website:
<http://www.sec.gov/divisions/corpfin/acctdis120105.pdf>.

Note 6. Collaborative Arrangements and Licensing Arrangements, page F-28

Out-Licensing Arrangements; Royalty Sharing Arrangements, page F-36

7. Please provide us with your analysis under EITF No. 88-18 to identify whether you should classify the payments from Drug Royalty USA, Inc. for future royalty rights as debt or as deferred revenue. Your analysis should include, but not be limited to, the points that follow.
 - Tell us whether you have any identification with the sold royalties or other continuing involvement under the Macugen license agreement, as you disclose that you are eligible to receive future milestone payments from Eyetech under the related license agreement.
 - Tell us whether you have the equivalent of patent defense rights related to the technology licensed to Eyetech and whether such rights would represent a form of continuing involvement.

Once you have performed the above analysis, if you determine that the \$8.0 million and \$7.0 million payments received to date from Drug Royalty USA, Inc. are not debt or deferred income under EITF No. 88-18, please clarify for us why immediate revenue recognition is appropriate under SAB No. 104.

* * * *

Please provide us the information requested within 10 business days of the date of this letter or tell us when you will provide a response prior to the expiration of the 10-day period. Please furnish a letter with your response that keys your response to our comments. Detailed letters greatly facilitate our review. You should furnish the letter to

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us via EDGAR under the form type label CORRESP. Please understand that we may have additional comments after reviewing your response to our comments.

We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filing to be certain that they have provided all information required under the Securities Exchange Act of 1934 and that they have provided all information investors require for an informed investment decision. Since the company and its management are in possession of all facts relating to a company's disclosure, they are responsible for the accuracy and adequacy of the disclosures they have made.

In connection with responding to our comments, please provide, in your letter, a statement from the company acknowledging that:

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

In addition, please be advised that the Division of Enforcement has access to all information you provide to the staff of the Division of Corporation Finance in our review of your filing or in response to our comment on your filing.

You may contact Amy Bruckner, Staff Accountant, at (202) 551-3657, or Mary Mast, Senior Accountant, at (202) 551-3613 if you have questions regarding comments on the financial statements and related matters. In this regard, please do not hesitate to contact me at (202) 551-3679.

Sincerely,

Jim B. Rosenberg
Senior Assistant Chief Accountant