



DIVISION OF
CORPORATION FINANCE

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

July 29, 2011

Via E-mail

Dr. Stanley Crooke
Chairman of the Board, President and Chief Executive Officer
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Re: Isis Pharmaceuticals, Inc.
Form 10-K for the Year Ended December 31, 2010
Filed March 1, 2011
Form 10-Q for the Quarterly Period Ended March 31, 2011
Filed May 6, 2011
Schedule 14A
Filed April 28, 2011
File No. 000-19125

Dear Dr. Crooke:

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 respond to this letter within 10 business days by providing the requested information or by advising us when you will provide the requested response. If you do not believe a comment applies to your facts and circumstances, please tell us why in your response. Please furnish us a letter on EDGAR under the form type label CORRESP that keys your responses to our comments.

After reviewing the information provided, we may raise additional comments and/or request that you amend your filing.

Form 10-K for the Year Ended December 31, 2010

Business

Collaborative Arrangements and Licensing Agreements, page 17

1. Please provide proposed disclosure to be included in future periodic reports to include the following additional information of your November 2001 agreement with OncoGenex and your January 2008 agreement with Genzyme:
 - o All material rights conferred and obligations assumed for and by both parties to the agreements,
 - o The nature of material patents and their jurisdiction and expiration dates, know-how or other intellectual property licensed or transferred in the agreements,

- Geographic, product, indication and other forms of exclusivity provided for in the agreements,
- The provisions regarding the termination of the agreements, and
- The duration of the agreements including the effect of patent expirations or marketing exclusivity, as applicable.

Explain whether the company was a party to or how the company otherwise consented to the December 2009 agreement transferring the rights to distribute OGX-011 to Teva. Indicate whether Teva was granted exclusive or more limited rights to the product and provide the same information regarding this agreement as requested above regarding the Genzyme and OncoGenex agreements.

Form 10-Q for the Quarterly Period Ended March 31, 2011
Notes to Condensed Consolidated Financial Statements

2. Significant Accounting Policies

Revenue Recognition

Research and development revenue under collaborative agreements, page 6

2. Please provide proposed disclosure to be included in future periodic reports that addresses the following for each arrangement under which you may earn milestone revenue in accordance with ASC 605-28-50-2:
 - A description of each milestone and related contingent consideration; and,
 - A determination of whether each milestone is considered substantive.

Schedule 14A filed April 28, 2011

Cash Bonus – At Risk, page 39

Cash Bonus, page 39

3. Please provide proposed disclosure to be included in future periodic reports to include the following additional information regarding the NEOs other than the CEO;
 - The specific MBO percentages employed for each NEO,
 - The specific individual success factors employed for each NEO, and
 - The evaluation of each NEO's individual performance for the purpose of setting the applicable individual success factors including the specific facts and results considered by the CEO and the Committee.

We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filings to be certain that the filings include the information the Securities Exchange Act of 1934 and all applicable Exchange Act rules require. 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 responding to our comments, please provide a written statement from the company acknowledging that:

- the company is responsible for the adequacy and accuracy of the disclosure in the filings;

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- staff comments or changes to disclosure in response to staff comments do not foreclose the Commission from taking any action with respect to the filings; 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.

Please contact Kei Nakada, Staff Accountant, at (202) 551-3659 or Gus Rodriguez, Accounting Branch Chief, at (202) 551-3752, if you have questions regarding the processing of your response as well as any questions regarding comments on the financial statements and related matters. You may contact Johnny Gharib, Staff Attorney, at (202) 551-3170 or Jeff Riedler, Assistant Director, at (202) 551-3715 with questions on any of the other comments. In this regard, do not hesitate to contact me at (202) 551-3679.

Sincerely,

/s/ Jim B. Rosenberg

Jim B. Rosenberg
Senior Assistant Chief Accountant