



DIVISION OF  
CORPORATION FINANCE

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

September 9, 2011

Via E-mail

Mr. B. Lynne Parshall  
Chief Operating Officer and Chief Financial 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 Mr. Parshall:

We have reviewed your August 12, 2011 response to our July 29, 2011 letter and have the following comment.

Please respond to this letter within ten business days by providing the requested information or by advising us when you will provide the requested response. Please furnish us a letter on EDGAR under the form type label CORRESP that keys your response to our comment.

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

Form 10-Q for the Quarterly Period Ended March 31, 2011  
Financial Statements  
Collaborative Arrangements and Licensing Agreements

1. We acknowledge your response to comment two. However, we believe that disclosure of each revenue milestone that you may potentially earn under the existing agreements is required under ASC 605-28-50-2. Accordingly, please revise your proposed disclosure to describe each milestone and related contingent consideration. In addition, if true, please also revise your proposed disclosure to clarify that you consider all potential milestones to be substantive.

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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 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