



DIVISION OF  
CORPORATION FINANCE

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

October 13, 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 completed our review of your filings. We remind you that our comments or changes to disclosure in response to our comments do not foreclose the Commission from taking any action with respect to the company or 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. We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filing to be certain that the filing includes the information the Securities Exchange Act of 1934 and all applicable rules require.

Sincerely,

/s/ Gus Rodriguez

Gus Rodriguez  
Accounting Branch Chief