



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

DIVISION OF
CORPORATION FINANCE

July 14, 2014

Via E-mail

Patrick R. O'Neil, Esq.
Senior Vice President and General Counsel
Isis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

**Re: Isis Pharmaceuticals, Inc.
Form 10-K for the Fiscal year Ended December 31, 2013
Filed March 3, 2014
File No. 000-19125**

Dear Mr. O'Neil:

We have completed our review of your filing. 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/ Jeffrey P. Riedler

Jeffrey P. Riedler
Assistant Director