

October 31, 2005

VIA FACSIMILE & EDGAR

Securities and Exchange Commission
Division of Corporation Finance
450 Fifth Street, NW
Washington, DC 20549

RE: Isis Pharmaceuticals, Inc.
Form S-3 Registration Statement No. 333-128156

Ladies and Gentlemen:

Pursuant to Rule 461 of Regulation C of the Securities Act of 1933, as amended, the undersigned registrant hereby requests that the Commission take appropriate action to cause the above-referenced Registration Statement No. 333-128156 to become effective at 5:00 p.m. Eastern Time on November 1, 2005 or as soon thereafter as is practicable.

In addition, the undersigned hereby acknowledges that:

- Should the Commission or the staff, acting pursuant to delegated authority, declare the filing effective, it does not foreclose the Commission from taking any action with respect to the filing;
- The action of the Commission or the staff, acting pursuant to delegated authority, in declaring the filing effective, does not relieve the company from its full responsibility for the adequacy and accuracy of the disclosure in the filing; and
- The company may not assert this action as a defense in any proceeding initiated by the Commission or any person under the federal securities laws of the United States.

Very truly yours,

ISIS PHARMACEUTICALS, INC.

By: /s/ Patrick O'Neil
Patrick O'Neil, Esq.
Associate General Counsel

cc: B. Lynne Parshall, Esq.
Grantland E. Bryce, Esq.
