

October 28, 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.

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.
