

Via Facsimile and U.S. Mail
Mail Stop 6010

September 9,

2005

B. Lynne Parshall, Esq.
Executive Vice President
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, California 92008

Re: Isis Pharmaceuticals, Inc.
Registration Statement on Form S-3
Filed September 7, 2005
File Number 333-128156

Dear Ms. Parshall:

This is to advise you that we have undertaken a limited review of the above referenced registration statement to resolution of your pending confidential treatment request. After any issues that arise during our examination of the request have been satisfied, we will consider your request for acceleration of the effective date of the registration statement.

Where indicated, we think you should revise your document in response to these comments. If you disagree, we will consider your explanation as to why our comment is inapplicable or a revision is unnecessary. Please be as detailed as necessary in your explanation. In some of our comments, we may ask you to provide us with supplemental information so we may better understand your disclosure. After reviewing this information, we may or may not raise additional comments.

* * *

We urge all persons who are responsible for the accuracy and adequacy of the disclosure in the filings reviewed by the staff to be certain that they have provided all information investors require for an informed decision. Since the company and its management are in possession of all facts relating to a company's disclosure, they are responsible for the accuracy and adequacy of the disclosures they have made.

Notwithstanding our comments, in the event the company requests acceleration of the effective date of the pending registration statement, it should furnish a letter, at the time of such request, acknowledging 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.

In addition, please be advised that the Division of Enforcement has access to all information you provide to the staff of the

Division of Corporation Finance in connection with our review of your filing or in response to our comments on your filing.

We will consider a written request for acceleration of the effective date of the registration statement as a confirmation of the fact that those requesting acceleration are aware of their respective responsibilities under the Securities Act of 1933 and the Securities Exchange Act of 1934 as they relate to the proposed public offering of the securities specified in the above registration statement. We will act on the request and, pursuant to delegated authority, grant acceleration of the effective date.

We direct your attention to Rules 460 and 461 regarding requesting acceleration of a registration statement. Please allow adequate time after the filing of any amendment for further review before submitting a request for acceleration. Please provide this request at least two business days in advance of the requested effective date.

Please contact Albert Lee at (202) 551-3654 or me at (202) 551-3715 with any questions.

Sincerely,

Jeffrey P. Riedler
Assistant Director

cc: Julie M. Robinson, Esq.
Cooley Godward LLP
4401 Eastgate Mall
San Diego, CA 92121

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