

DC



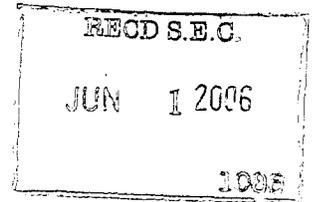
DIVISION OF
CORPORATION FINANCE

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549-3010



06038320

May 31, 2006



Patrick R. O'Neil
Associate General Counsel
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Act: 1934
Section: _____
Rule: 14A-8
Public
Availability: 5/31/2006

Re: Isis Pharmaceuticals, Inc.
Incoming letter dated April 11, 2006

Dear Mr. O'Neil:

This is in response to your letter dated April 11, 2006 concerning the shareholder proposal submitted to Isis by Raymond S. Marine. Our response is attached to the enclosed photocopy of your correspondence. By doing this, we avoid having to recite or summarize the facts set forth in the correspondence. Copies of all of the correspondence also will be provided to the proponent.

In connection with this matter, your attention is directed to the enclosure, which sets forth a brief discussion of the Division's informal procedures regarding shareholder proposals.

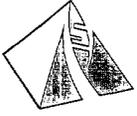
Sincerely,

Eric Finseth
Attorney-Adviser

Enclosures

cc: Raymond S. Marine
2327 Indian Ridge Estates Dr.
Mobile, AL 36695

PROCESSED
JUN 23 2006
B
THOMSON
FINANCIAL



ISIS
PHARMACEUTICALS

1896 Rutherford Road Carlsbad, CA 92008
p 760.931.9200 f 760.603.4650 www.isispharm.com info@isisph.com

April 11, 2006

U.S. Securities and Exchange Commission
Division of Corporation Finance
Office of Chief Counsel
450 Fifth Street, N.W.
Washington, D.C. 20549

RECEIVED
2006 APR 12 AM 3:48
OFFICE OF CHIEF COUNSEL
DIVISION OF CORPORATION FINANCE

Re: Proxy Statement of Isis Pharmaceuticals, Inc.;
Request to Exclude Pursuant to Rule 14a-8(i)(8)

Ladies and Gentlemen:

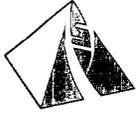
I am writing on behalf of Isis Pharmaceuticals, Inc., a Delaware Corporation ("Isis"), in connection with a possible request from one of Isis' stockholders. On April 8, 2006, Isis received a letter from Mr. Raymond S. Marine, in which Mr. Marine requested that Isis' Nominating, Governance and Review Committee consider him as a candidate to serve on Isis' Board of Directors.

As part of his letter, Mr. Marine states that he would like to "... run as a member of the board for Isis Pharmaceuticals, Inc. in the up coming (*sic*) proxy vote." Mr. Marine's letter could be interpreted as a proxy solicitation, and therefore, without admission on its part, Isis has prepared this No Action Letter. For your information, I have included a copy of Mr. Marine's request with this letter.

Isis believes Mr. Marine's notice failed to satisfy a number of the eligibility and procedural requirements set forth in parts (b) and (e) of Rule 14a-8 of the Securities Exchange Act of 1934. Specifically, the notice:

- Was not received by Isis by the deadline for submitting a proposal, as disclosed in Isis' Definitive Proxy Statement filed with the SEC on April 19, 2005;
- Failed to demonstrate to us that he was eligible to submit a shareholder proposal, since he is not a stockholder of record; and
- Did not contain a written statement by him that he intended to hold his Isis securities through the date of the Stockholders Meeting.

Isis respectfully submits that Mr. Marine's failure to meet the submission deadline is a fatal error. In fact, he did not send his request until after Isis had already filed and mailed its Definitive Proxy Statement.



ISIS

PHARMACEUTICALS

In addition, Isis believes that it is entitled to exclude Mr. Marine's proposal pursuant to Rule 14a-8(i)(8) because the proposal relates to an election for membership on Isis' Board of Directors. Accordingly, on behalf of Isis, I respectfully request exemptive relief from the provisions of Rule 14a-8 to permit Isis to exclude Mr. Marine's proposal.

I appreciate the Staff's consideration of this matter. Please do not hesitate to contact me at (760) 603-2732 with any questions.

Sincerely,

Patrick R. O'Neil, Esq.
Associate General Counsel
Isis Pharmaceuticals, Inc.

Enclosure

Mr. Raymond S. Marine
2327 Indian Ridge Estates Dr.
Mobile, Alabama 36695
ph: (251)-639-0046
fax: (251)-639-5187

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, California 92008-7208

ph: (760)-931-9200
fax: (760)-603-2700

Dear Sir:

I want to nominate myself to run as a member of the board for Isis Pharmaceuticals in the up coming proxy vote.

I meet all the qualifications that were stated in your article. If you need more information from me, or if I need to submit something else, please notify me immediately.

Thank you,

Raymond S. Marine

Raymond S. Marine

**DIVISION OF CORPORATION FINANCE
INFORMAL PROCEDURES REGARDING SHAREHOLDER PROPOSALS**

The Division of Corporation Finance believes that its responsibility with respect to matters arising under Rule 14a-8 [17 CFR 240.14a-8], as with other matters under the proxy rules, is to aid those who must comply with the rule by offering informal advice and suggestions and to determine, initially, whether or not it may be appropriate in a particular matter to recommend enforcement action to the Commission. In connection with a shareholder proposal under Rule 14a-8, the Division's staff considers the information furnished to it by the Company in support of its intention to exclude the proposals from the Company's proxy materials, as well as any information furnished by the proponent or the proponent's representative.

Although Rule 14a-8(k) does not require any communications from shareholders to the Commission's staff, the staff will always consider information concerning alleged violations of the statutes administered by the Commission, including argument as to whether or not activities proposed to be taken would be violative of the statute or rule involved. The receipt by the staff of such information, however, should not be construed as changing the staff's informal procedures and proxy review into a formal or adversary procedure.

It is important to note that the staff's and Commission's no-action responses to Rule 14a-8(j) submissions reflect only informal views. The determinations reached in these no-action letters do not and cannot adjudicate the merits of a company's position with respect to the proposal. Only a court such as a U.S. District Court can decide whether a company is obligated to include shareholder proposals in its proxy materials. Accordingly a discretionary determination not to recommend or take Commission enforcement action, does not preclude a proponent, or any shareholder of a company, from pursuing any rights he or she may have against the company in court, should the management omit the proposal from the company's proxy material.

May 31, 2006

**Response of the Office of Chief Counsel
Division of Corporation Finance**

Re: Isis Pharmaceuticals, Inc.
Incoming letter dated April 11, 2006

The submission nominates the proponent for membership on Isis' board of directors.

It is unclear whether the submission involves only a rule 14a-8 issue, or, also questions regarding nomination procedures, a matter we do not address. To the extent the submission involves a rule 14a-8 issue, there appears to be some basis for your view that Isis may exclude it under rule 14a-8(i)(8), as relating to an election to Isis' board of directors, and we will not recommend enforcement action to the Commission if Isis omits the proposal from its proxy materials in reliance on rule 14a-8(i)(8). To the extent the submission involves a question of Isis' nomination procedures, rule 14a-8 would not be implicated. In reaching this position, we have not found it necessary to address the alternative bases for omission upon which Isis relies.

Sincerely,



Mary Beth Breslin
Special Counsel