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Office of the Secretary, PCAOB
1666 K Street, N.W.
Washington, D.C. 20006-2803

Re: PCAOB Rulemaking Docket Matter No. 37
Concept Release on Auditor Independence and Audit Firm Rotation

Ladies and Gentleman:

Isis Pharmaceuticals Inc. (NASDAQ: ISIS), a large accelerated filer, is the leading company in antisense drug discovery and development, exploiting a novel drug discovery platform we created to generate a broad pipeline of first-in-class drugs. We maximize the value of the drugs we discover by putting them in the hands of leading pharmaceutical companies with late-stage development, commercialization and marketing expertise, such as Biogen Idec, Bristol-Myers Squibb, Genzyme, a Sanofi company, GlaxoSmithKline, and Eli Lilly and Company.

We appreciate the opportunity to comment on the Concept Release on Auditor Independence and Audit Firm Rotation issued by the Public Company Accounting Oversight Board (PCAOB) in August 2011. The purpose of the Concept Release is to improve auditor objectivity, professional skepticism and independence with the intention of increasing overall audit quality. We support the PCAOB's interest in improving auditor independence and objectivity however, we do not support the proposal for mandatory audit firm rotation. We do not believe that such rotations will improve audit quality or enhance auditor independence and objectivity. In fact, we believe that such mandatory rotations will diminish audit quality in the early years of an engagement, drive up costs, and undermine the function of the audit committee.

Our audit firm's knowledge of our industry and the experience of the members of the audit team are critical components of achieving a quality audit of our financial statements. An auditor achieves a profound understanding of a complex company, like ours, through active engagement over an extended period of time. The cumulative value of this institutional knowledge should not be underestimated. Attaining a deeper understanding of the company, its philosophy, policies, standards, goals, processes, systems and culture is critical to audit effectiveness and takes many years to achieve.

Isis operates in a highly specialized environment. The transactions we enter into typically relate to collaboration projects that are complex and unique for each of our partnerships. We use our industry experience and professional judgment to analyze and determine the appropriate revenue recognition for our transactions. Our conclusions require us to assess our performance obligations, the overall relationship with our partner and our historical experience in discovering and developing drugs. Accordingly, the accounting we do in our industry can be very complex and requires a significant amount of judgment. Therefore we believe it is important that

our auditors understand our industry and our business in order to validate the various assumptions we make. Audit firms, for competitive and other reasons, naturally specialize in different industries. As a result, they are not all able to develop the knowledge and expertise required to effectively audit the life sciences industry. Mandatory audit firm rotation would result in the periodic loss of auditors who have developed specialized industry and company knowledge, which would decrease their ability to perform a high quality audit. We believe that specialized knowledge and expertise significantly enhances the quality of the audit.

In addition, we believe that our audit costs will increase significantly during the first few years because a new audit firm would be required to invest time to educate themselves about the company, its operations and business practices. The 2003 GAO study estimated that there would be an increase of 20% in audit fees as a result of a mandatory audit firm rotation model¹. This cost impact reflects the cost the audit firms incur, and pass on to us, resulting from the inevitable inefficiency of performing a complex audit process for the first time with a new client.

There will also be indirect costs incurred by our company because management will have to devote time and resources to responding to questions and explaining significant accounting decisions made in prior years. This will be a distraction and a disruption of our operations. It will be a burden to all levels within our organization from the audit committee, senior management, accounting staff, IT department and legal department. An inordinate number of hours of internal company time will be spent to orient new auditors and help them to become familiar with our business and financial reporting controls and processes.

We understand the importance of improving independence and objectivity in the selection of auditors. A primary function of our audit committee is to ensure the independence of the audit function. The audit committee accomplishes this through exercising its direct responsibility for appointing, compensating, retaining and overseeing the work performed by the independent auditor. The required rotation of the audit firm would diminish the audit committee's responsibility to appoint and retain a qualified independent auditor. Under the proposal, the audit committee would no longer have the ability to retain an audit firm beyond a specified time frame. The availability of qualified audit firms would be limited and force our audit committee into potentially appointing a less knowledgeable and therefore less qualified audit firm to our company's engagement. This would decrease audit quality and expose the company and its stakeholders to unnecessary risks.

The PCAOB already plays a key role in ensuring auditor independence through its ongoing inspection and enforcement responsibilities, which provide significant oversight of the auditors. In addition, the Sarbanes Oxley Act ("SOX") established a number of rules regarding audit firms and audit committees. The enduring value of SOX and the rules adopted by the PCAOB involve those rules that:

- Require the mandatory rotation of coordinating audit partners;
- Prohibit audit firms from providing services that may lead to a conflict of interest or otherwise jeopardize their independence (e.g., bookkeeping services, valuation services, internal audit services);
- Require the pre-approval by audit committees of services provided by the auditor;
- Require audit firms to communicate certain matters to audit committees (e.g., the auditor's responsibilities regarding the audit, significant findings from the audit, the selection and application of accounting policies and material changes thereto, etc.);
- Require that audit committees are adequately funded; and

¹ Government Accountability Office, November 2003, *Required study on the potential effects of mandatory audit firm rotation*, page 6.

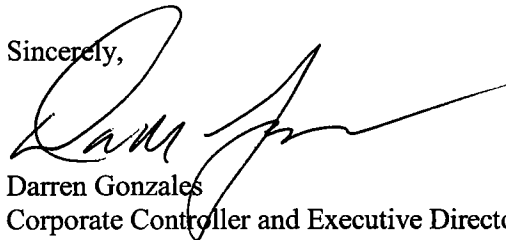
- Empower audit committees with the authority to engage outside advisors as they deem necessary or advisable in order to perform their duties.

We believe the existing rules provide appropriate guidance and an equitable framework for audit committees to help ensure the independence and objectivity of their audit firms. In particular, rotating the engagement partner every five years provides stability and retains institutional knowledge and expertise while also adding a fresh perspective to promote high quality audits. The costs associated with the automatic rotation of an audit firm far outweigh any potential benefits.

Independence is already a key focus of the audit firms, which must adhere to audit standards and establish a mindset within the firm that independence, professional skepticism, and objectivity are imperative. The reputation and integrity of the firms who audit financial statements are the most valuable assets they possess. Accordingly, it is not reasonable to believe auditors would, in today's post-Enron era of increased regulation and heightened litigation and oversight, jeopardize both their firms' reputations and financial position due to management pressure over the accounting for a particular transaction or maintaining a client relationship.

Isis Pharmaceuticals, Inc. appreciates having the opportunity to express our views on the Concept Release on Auditor Independence and Audit Firm Rotation. For the reasons described above, we do not believe that the PCAOB should move forward with a mandatory audit firm rotation requirement. Rather, the PCAOB should continue its efforts to improve the effectiveness of the current audit standards through inspection and other currently existing means. We appreciate the opportunity to comment on the Release and thank you for your consideration of our views.

Sincerely,



Darren Gonzales
Corporate Controller and Executive Director, Accounting
Isis Pharmaceuticals