



ISIS
PHARMACEUTICALS

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SENT VIA INTERNET COMMENT FORM

March 29, 2013

Securities and Exchange Commission
100 F Street NE
Washington, DC 20549

Dear Ladies and Gentlemen:

I am the Chief Financial Officer of Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) and I would like to provide my comments and concerns about the proposed rule change in release No. 34-69030 (File No. SR-NASDAQ-2013-032) requiring all listed companies to establish and maintain an internal audit function. I appreciate and understand the need for sound financial controls and we take very seriously our obligations to maintain effective systems of both disclosure controls and procedures and internal controls over financial reporting. I believe our efforts to comply with the requirements of the Sarbanes-Oxley Act of 2002 ("SOX") combined with the oversight and communications performed by our independent auditors achieve the objectives of the proposed rule without having to establish and maintain an internal audit function.

The required ongoing maintenance and annual evaluation we are already performing for SOX requires us to devote a significant amount of money and internal and external resources. The maintenance and evaluation of our internal controls helps us to identify potential weaknesses and deficiencies in advance of a system breakdown, thereby facilitating the continuous, orderly and timely flow of information within our company, to our audit committee and, ultimately, to investors and the marketplace.

We utilize a third party service provider to perform testing of our internal controls over financial reporting, which I believe adds another level of objectiveness to our assessment. Although this service provider does not report directly to the audit committee, they are definitely empowered to report matters directly to the audit committee should the need arise. I also note that we have an anonymous hotline should anyone involved in the financial reporting process desire to report irregularities in that manner to the audit committee.

In addition to the communication achieved under SOX, the Public Company Accounting Oversight Board requires our independent auditor to perform procedures to audit our internal controls and communicate to our audit committee significant deficiencies and material weaknesses, any additional information included in management's report on internal control, fraud and illegal acts involving senior management, and fraud and illegal acts that cause a material misstatement of the financial statements. As such, our independent auditors regularly meet with members of our management team and our audit committee, including



executive sessions with the audit committee without management present, to discuss our internal controls and any fraudulent or illegal acts.

One of the key elements of our internal controls over financial reporting is our entity level controls, which we maintain and evaluate as part of our SOX compliance and is included in our independent auditor's annual audit of our internal controls over financial reporting. Our entity level controls include but are not limited to:

- Our risk assessment process,
- Policies that address significant business controls and risk management practices,
- Tone at the top,
- Board/audit committee reporting, and
- Fraud prevention/detection controls and analytical procedures.

Our entity-level controls have a pervasive influence throughout our organization and achieve the following benefits:

- A reduction in the likelihood of a negative risk event by establishing and reinforcing the infrastructure that sets the control consciousness of the organization,
- Broad coverage of the risks over financial reporting and operations, and
- Reinforcement for all stakeholders of the importance of internal controls to the success of the business.

Furthermore, we currently incur a considerable amount of expense to comply with public company rules and regulations. The activities and costs associated with our compliance are significant, particularly for a company like Isis Pharmaceuticals, a pre-profit company investing heavily in the research and development of new drugs to treat human diseases. Proposals that limit this rule change to large-filers only do not satisfy our objections, because Isis, like many life sciences companies, is a large accelerated filer by virtue of our market capitalization and not our revenue. Our current and future value is derived substantially from our pipeline of drug candidates.

In addition to the existing compliance requirements associated with being a public company, we operate in a highly regulated environment. The Food and Drug Administration (FDA) and its foreign equivalents impose regulatory standards on our operations, therefore the proposed rule as currently written would create duplicate work throughout our company as several compliance activities are managed by our regulatory, clinical development, manufacturing and health and safety organizations. As a result, our company would incur additional costs and our internal resources would be diverted from their normal activities in order to comply with the new rule.

Further, there is no evidence provided in the release that demonstrates that the cost of adding an internal audit function will produce significant value in the form of improved controls over what exists today or that it would improve investor confidence. More regulation, only to offer form over substance, is not



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helpful to listed companies, nor is it helpful to overall domestic economic development because of the additional regulatory cost burden. It may also unfairly provide a cost-advantage to foreign-listed companies, which will not have to incur the additional and unnecessary expense. As such, it is my opinion that the proposed rule change is unnecessary.

Prior to making a decision on this proposal, I think it would be prudent to review the results of the GAO study required by the Dodd-Frank Wall Street Reform and Consumer Protection Act, which is expected to be completed later this year, to evaluate whether exempt issuers have fewer or more restatements, and how their cost of capital compares with issuers subject to section 404(b).

Thank you for the opportunity to express my opinion.

Respectfully,

Elizabeth L. Hougen
Chief Financial Officer
Isis Pharmaceuticals, Inc.