June 21, 2007

United States Securities and Exchange Commission
Division of Corporate Finance
Attn: Jim B. Rosenberg, Senior Assistant Chief Accountant
100 F Street, NE
Washington, D.C. 20549

Re: Isis Pharmaceuticals, Inc.
Form 10-K for the fiscal year ended December 31, 2006
File No. 000-19125

Dear Mr. Rosenburg:

On behalf of Isis Pharmaceuticals, Inc., enclosed for electronic filing via EDGAR pursuant to the Securities Act of 1933, please find responses to your comments in reference to the Company's Form 10-K for the fiscal year ended December 31, 2006, File No. 000-19125.

Based on our responses to your comments, we believe there are no material changes required to our Form 10-K for the fiscal year ended December 31, 2006. For the responses that further clarify our existing disclosure, we will include the additional clarifying language in the disclosures contained in our Form 10-Q for the quarter ending June 30, 2007.

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

CRITICAL ACCOUNTING POLICIES, PAGE 54

1. *Your discussion of critical accounting policies does not explain how the estimates have affected your results of operations. Provide to us proposed disclosure that quantifies how accurate your estimates and assumptions have been in the past. Refer to Release No. 33-8350.*

In response to your inquiry about our critical accounting policies, we propose to add the sentences below to our existing disclosure to address your comment. Please note that for each addition below, we have included a reference to Attachment A, which contains a revised version of our entire Critical Accounting Policies.

Critical Accounting Policies (page A-1, lines 15-17):
Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results.

Critical Accounting Policies—Revenue Recognition (page A-2, lines 13-14):
To date our estimates have not required material adjustments.

Critical Accounting Policies—Estimated Liability for Clinical Development Costs (page A-5, lines 38-39):
Our historical accrual estimates have not been materially different from our actual amounts.

Critical Accounting Policies—Segment Information (page A-6, lines 9-11):
We have not made material changes to our allocation methodologies since we began reporting segment financial information and results.

Critical Accounting Policies—Stock-Based Compensation (page A-7, lines 8-9):
There were no material changes to our estimated forfeitures in fiscal 2006.

2. *In addition to the above, please provide us with additional information, in a disclosure-type format, regarding the information that you rely on in estimating your continuing obligations under your agreements with Antisense Therapeutics, Ltd., Lilly, OncoGenex and Pfizer. Specifically, tell us how you estimate your remaining performance obligation under each arrangement and provide us with proposed disclosure for Note 6 that details the following:*

   - *The amount of the milestone payments or upfront fees received, the amount recognized within revenue for each financial statement period presented, and the related amortization period for any amounts deferred; and*

   - *Whether or not you have changed your estimate of the remaining performance period under each arrangement and how such a change in estimate impacted your results of operations for the financial statement periods presented.*

In response to your inquiry about our estimates of certain continuing obligations, we propose to add the sentences below to our existing disclosure to address your comment. Please note that we have included a reference to Attachment A, which contains a revised version of our entire Critical Accounting Policies.

Critical Accounting Policies— Revenue Recognition (page A-2, lines 16-26):
Our collaborative agreements typically include a research and/or development project plan that includes activities to be performed in the collaboration and the party responsible for performing them. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. When our collaborators have asked us to continue performing work in a collaboration

beyond the initial period of performance, we have extended our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue.

In response to your comment in the first bullet point, to the extent the information you requested was not in our existing disclosure, the following responses provide the additional information. Please note that we have included a reference to Attachment B, which contains revised sections of Note 6. In Attachment B, to the extent that our existing disclosure addressed your comment, we italicized the text to highlight the information for you.

Antisense Therapeutics Limited (page B-2, lines 34-39):
The initial ATL common stock Isis received had a value of $2.8 million, and Isis recognized this amount into revenue ratably over the five-year period of performance under the collaboration, which ended in November 2006. There were no changes in Isis' period of performance. The amount of deferred revenue was $0 and $506,000 at December 31, 2006 and 2005, respectively.

Eli Lilly and Company (page B-1, lines 41-43 and page B-2, lines 1-4):
Isis amortized the $1.1 million license fee related to LY2181308 over a two-year period, which ended in June 2004. The two-year period corresponded to Isis' period of performance for LY2181308 and there were no changes to the period of performance. In September 2004, Isis recognized $750,000 associated with the license fee it received for LY2275796. Lilly is responsible for the preclinical and clinical development of LY2275796 and Isis has no performance obligations for this drug.

OncoGenex Technologies Inc.

(page B-3, lines 21-23):
OncoGenex is responsible for the preclinical and clinical development of the drug **and Isis has no performance obligations**. OncoGenex issued to Isis $**750,000 of** OncoGenex securities as payment for an upfront fee.

(page B-3, lines 30-32):
Under the terms of the agreement, OncoGenex is responsible for the preclinical and clinical development of the drugs **and Isis has no performance obligations**.

(page B-3, lines 35-37):
OncoGenex paid Isis an upfront fee **of $750,000** with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock.

(page B-3, lines 39-41):
As of December 31, 2006, OncoGenex had not met any of the milestones that would result in payments related to OGX-427.

Pfizer, Inc.

(page B-1, lines 8-12):
Under the terms of the agreement, Isis received an upfront technology access fee of $1.0 million and amortized this amount over the one year period of Isis' performance based on the research plan included in the agreement, which ended in April 2006. There were no changes in Isis' period of performance. The amount of deferred revenue was $0 and $333,000 at December 31, 2006 and 2005, respectively.

(page B-1, lines 18-20):
For the years ended December 31, 2006, 2005 and 2004, Isis recognized revenue of $408,000, $2.2 million and $0, respectively, related to this collaboration.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

NOTE 1. ORGANIZATION AND SIGNIFICANT ACCOUNTING POLICIES, PAGE F-7

3. Based on your disclosure herein and on page 57 of your Management's Discussion and Analysis, it appears that you capitalize inventory costs related to drugs that you utilize in clinical development activities. Please provide us with additional information, in a disclosure-type format, that clarifies why you believe your accounting policy is appropriate. Please address SFAS No. 2 or other literature as applicable.

In response to your inquiry about our capitalization policy for inventory, we propose to add the sentences below to our existing disclosure to address your comment. Please note that for each addition below, we have included a reference to Attachment A, which contains a revised version of our entire Critical Accounting Policies.

Critical Accounting Policies—Valuation of Inventory

(page A-5, lines 5-8):
In accordance with SFAS 2, *Accounting for Research and Development Costs*, we capitalize the costs of raw materials that we purchase for use in producing our drugs because, until we use these raw materials, they have alternative future uses.

(page A-5, lines 10-14):
Each of our raw materials can be used in multiple products and, as a result, have future economic value independent of the development status of any single drug. For example, if one of our drugs failed, the raw materials allocated for that drug have economic value for other drugs that we manufacture.

NOTE 4. STOCKHOLDERS' EQUITY, PAGE F-19

4. *Please provide us with your analysis, in a disclosure-type format, as to whether the warrants issued in your April 2006 Symphony GenIsis Holdings LLC transaction qualify as a derivative instrument within the scope of SFAS No. 133, which would necessitate that you account for those warrants at fair value and record changes in that fair value within earnings. Additionally, please provide us with an analysis under EITF No. 00-19 that supports your classification of these warrants as an equity instrument. The registration rights agreement filed as Exhibit 10.3 to your March 31, 2006 Form 10-Q appears to indicate that you have an obligation to maintain the effectiveness of the related registration statement, as well as other Exchange Act timely reporting obligations. Please refer to paragraphs 14, 18 and 25 to EITF No. 00-19.*

In response to your inquiry about the warrants issued to Symphony GenIsis Holdings LLC, we propose to add the sentences below to our existing disclosure to address your comment. Please note that for each addition below, we have included a reference to Attachment C, which contains a revised version of the Symphony GenIsis Holdings warrant disclosure.

Note 4—Warrants

(page C-1, lines 5-6):
These warrants expire on April 7, 2011 and can be settled with unregistered shares of Isis' common stock.

(page C-1, lines 38-46 and page C-2, lines 1-3):
In connection with the issuance of the warrants, Isis entered into a registration rights agreement with Symphony GenIsis Holdings LLC. Pursuant to the registration rights agreement, Isis filed a registration statement with the SEC covering the shares of common stock issuable upon exercise of the warrants. Isis is required to use commercially reasonable efforts to maintain the effectiveness of the registration statement over the term of the warrant.

Isis evaluated the provisions of the registration rights agreement and the warrant purchase agreement under EITF 00-19, *Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock*, and determined that the criteria for equity classification were met; therefore, the warrants were accounted for as part of stockholders' equity.

Below is our analysis under EITF 00-19, specifically, paragraphs 12-32, that supports our classification within stockholders' equity:

- The contract permits the company to settle in unregistered shares—the agreements allow for settlement in unregistered shares. Therefore this criterion is met.

- The company has sufficient authorized and unissued shares available to settle the contract after considering all other commitments that may require the issuance of stock during the maximum period the derivative contract could remain outstanding—at the time of the transaction, we had 100 million shares authorized and 11.7 million shares available to issue after subtracting the shares that were outstanding and the shares that were reserved for future issuance. Given the fact that the maximum number of shares that could be issued for the warrants is 4.25 million shares, this criterion is met.

- The contract contains an explicit limit on the number of shares to be delivered in a share settlement—the maximum number of shares of common stock issuable upon the exercise of the warrants is 4.25 million shares; therefore this criterion is met.

- There are no required cash payments to the counterparty in the event the company fails to make timely filings with the SEC— there are no cash payments, including liquidated damages, required if we fail to make timely filings with the SEC. Therefore this criterion is met.

- There are no required cash payments to the counterparty if the shares initially delivered upon settlement are subsequently sold by the counterparty and the sales proceeds are insufficient to provide the counterparty with full return of the amount due (that is, there are no cash settle "top off" or "make whole" provisions)—there are no cash settle "top off" or "make whole" provisions in the agreements, therefore this criterion is met.

- The contract requires net-cash settlement only in specific circumstances in which holders of shares underlying the contract also would receive cash in exchange for their shares—there are no provisions in the agreements that would require a net-cash settlement with the same or greater economic value as the net-share settlement and physical settlement options, therefore this criterion is met.

- There are no provisions in the contract that indicate that the counterparty has rights that rank higher than those of a shareholder of the stock underlying the contract—there are no provisions in the agreements that provide the counterparty with rights that rank higher than those of a shareholder of the stock underlying the contract, therefore this criterion is met.

- There is no requirement in the contract to post collateral at any point or for any reason—there are no provisions in the agreements that would require us to post collateral, therefore this criterion is met.

Based upon the above criteria that are contained in EITF 00-19, the combined financial instrument qualifies for classification within stockholders' equity.

5. *Please provide us with information that supports your decision to reclassify the warrant liability associated with your August 2005 private placement from liabilities to equity on your statement of financial position for the year ended December 31, 2005. Address in your response whether you have any continuing obligations similar to those in the preceding comment to keep an underlying registration statement effective and make timely Exchange Act filings.*

The application of EITF 00-19 involves the evaluation of many complex factors and in practice, registrants have used various methods to account for registration rights agreements. We analyzed the warrant and the registration rights agreement associated with our August 2005 private placement under EITF 00-19. Based on the application of EITF 00-19, we recorded the value of the warrant as a liability during the three months ended September 30, 2005. During the period from the instrument's inception until the reclassification of the instrument to equity, we recorded $2.1 million of interest income as we revalued the instrument as a liability. Upon the declaration of an effective registration statement in the fourth quarter of 2005, we reevaluated the financial instrument and determined that maintaining the effectiveness of the registration statement was within our control. As the likelihood of providing liquidated damages to the investors was not deemed probable in accordance with FASB Statement No. 5, *Accounting for Contingencies*, the financial instrument met the criteria under EITF 00-19 for equity classification. Therefore, we reclassified the warrant liability to equity during the fourth quarter of 2005, as recorded in our Form 10-K for the year ended December 31, 2005.

Please note that failure to timely file Exchange Act reports does not itself trigger liquidated damages. Rather, we have up to 90 days to make any necessary filings under the Securities Act to maintain the usefulness of the registration statement and avoid having to pay liquidated damages (see Section 6.3 and 6.7(b) of the securities purchase agreement). Furthermore, to date we have not paid any liquidated damages nor will we be required to pay any liquidated damages in the future because we are only required to maintain an effective registration statement through the second anniversary of the closing of the private placement (i.e. through August 23, 2007). Therefore, as of the date of this letter and after considering the 90-day grace period mentioned above, we will not have to pay liquidated damages under the agreement (see Section 6.4(a) of the securities purchase agreement). As a result, our position that timely filings are within our control and that the probability of paying liquidated damages was remote was correct. The consideration of probability to provide liquidated damages for the lack of an effective underlying registration statement is consistent with the guidance provided under FASB Staff Position No. EITF 00-19-2, *Accounting for Registration Payment Arrangements*.

In addition, based on the recent issuance of FASB Staff Position No. EITF 00-19-2, the accounting for the warrant as an equity instrument from its inception would have a consistent impact on our net stockholders' equity at December 31, 2005 and March 31, 2007.

6. *Please tell us how you viewed and accounted for the registration rights agreement related to both your December 31, 2005 private placement transaction and the Symphony GenIsis transaction in relation to EITF No. 05-4. Refer to the Division of Corporation Finance "Current Accounting and Disclosure Issues" Section II (B) – Classification and Measurement of Warrants and Embedded Conversion Features (New). You can find this at the following website: http://www.sec.gov/divisions/corpfin/acctdis120105.pdf.*

As denoted in the response to comment four, the registration rights agreement associated with the Symphony GenIsis transaction did not have an impact on the accounting for the warrant as there were no liquidated damages in the event that the Company fails to register the underlying.

We have considered the impact of the registration rights agreement associated with the warrants issued in the private placement of common stock in August 2005 and reached the conclusions outlined in the response to comment five.

NOTE 6. COLLABORATIVE ARRANGEMENTS AND LICENSING ARRANGEMENTS

OUT-LICENSING ARRANGEMENTS: ROYALTY SHARING ARRANGEMENTS, PAGE F-36

7. *Please provide us with your analysis under EITF No. 88-18 to identify whether you should classify the payments from Drug Royalty USA, Inc. for future royalty rights as debt or as deferred revenue. Your analysis should include, but not be limited to, the points that follow.*

   - *Tell us whether you have any identification with the sold royalties or other continuing involvement under the Macugen license agreement, as you disclose that you are eligible to receive future milestone payments from Eyetech under the related license agreement.*

   - *Tell us whether you have the equivalent of patent defense rights related to the technology licensed to Eyetech and whether such rights would represent a form of continuing involvement.*

   Once you have performed the above analysis, if you determine that the $8.0 million and $7.0 million payments received to date from Drug Royalty USA, Inc. are not debt or deferred income under EITF No. 88-18, please clarify for us why immediate revenue recognition is appropriate under SAB No. 104.

Background

Under our agreement with Drug Royalty USA, Inc. ("DRC"), we sold DRC a portion of our royalty rights in Macugen. We have the right to receive a royalty on Macugen pursuant to our license agreement with Eyetech Pharmaceuticals (now part of OSI

Pharmaceuticals Inc.) Macugen is a drug that was discovered and developed outside of Isis, but that is covered by a series of our patents which are broadly applicable to various types of oligonucleotide drugs. Our license agreement with Eyetech is a pure license agreement under which we licensed Eyetech the right to practice the necessary patents to develop and commercialize Macugen, with no obligations or performance from us, in exchange for an upfront fee, milestone payments and royalties. We do not, and did not, participate in any way in the development or commercialization of Macugen.

We do not, and did not, have any patent defense obligations under our agreement with Eyetech or DRC. Our license with Eyetech does not contain patent defense obligations for either party. Patent defense obligations are specifically addressed in Section 3.5(c) of our DRC agreement wherein we have the right, but not the obligation to defend the licensed patents. Further, in our Eyetech agreement, we have the right, but not the obligation, to prosecute and/or maintain the patent rights covered by the agreement. Although our DRC agreement provides that we will prosecute and/or maintain the patents covered by the agreement, DRC has no contractual right to recover payments it has already made if we fail to prosecute the licensed patents.

Sales of Future Revenues—Analysis under EITF 88-18

To determine if the sale of a portion of our royalty rights in Macugen to DRC should be classified as debt, the guidance contained in EITF 88-18 must be considered. If the presence of any one of the following six factors exists, there is a rebuttable presumption that classification of the proceeds as debt is appropriate.

- The transaction does not purport to be a sale (that is, the form of the transaction is debt)— This transaction was structured as a sale as specifically stated in section 1.1 of the Agreement for Sale and Assignment of Rights, "Isis hereby sells, assigns, transfers, set-over and conveys to DRC all right, title and interest in and to the Assigned Rights free and clear of any Encumbrances," Section 1.1 is further supported by section 3.8 which states that "Isis will treat its sale and assignment to DRC of the Assigned Rights pursuant to Section 1.1 as a sale and assignment on Isis' books and records." Given the structure of our DRC agreement, this transaction is a sale and therefore this factor is not present.

- The enterprise has significant continuing involvement in the generation of the cash flows due the investor (for example, active involvement in the generation of the operating revenues of a product line, subsidiary, or business segment)— In December 2001, we licensed certain patents to Eyetech Pharmaceuticals, Inc. in exchange for an upfront fee, milestone payments and royalties on sales of Macugen. As mentioned above, we did not, and do not, have any obligations under our agreement with Eyetech. Because the generation of cash flows due DRC (i.e., the royalty payments generated on the sales of Macugen) does not require any involvement or performance by us, this factor is not present.

- The transaction is cancelable by either the enterprise or the investor through payment of a lump sum or other transfer of assets by the enterprise —No such provisions are contained in our DRC agreement, therefore this factor is not present.

- The investor's rate of return is implicitly or explicitly limited by the terms of the transaction—There are no provisions in our DRC agreement that implicitly or explicitly limit DRC's rate of return, therefore this factor is not present.

- Variations in the enterprise's revenue or income underlying the transaction have only a trifling impact on the investor's rate of return—DRC's revenue is significantly impacted by the sales of Macugen by OSI (or its marketing partner Pfizer). Therefore, this factor is not present.

- The investor has any recourse to the enterprise relating to the payments due to the investor—DRC does not have recourse to the payments due to DRC from OSI related to Macugen. Therefore, this factor is not present.

Since none of the above factors are present, under the provisions of EITF 88-18, the proceeds from DRC should not be classified as debt.

Revenue Recognition under SAB 104

Since the payments received from DRC are not classified as debt, recognition of revenue needs to be analyzed. Because the payments we receive from DRC are contingent in nature, non-refundable and no further performance obligations exist, similar to payments for milestones, we feel that recognition of revenue upon receipt of the payment is appropriate. To further illustrate that treatment, we analyzed our agreement with DRC using the criteria in SAB 104:

- Persuasive evidence of an arrangement exists—The agreement between us and DRC represents persuasive evidence of the arrangement between the two companies. Therefore this criterion is met.

- Delivery has occurred or services have been rendered— We have no performance obligations under our DRC agreement, except our obligation to prosecute the patents associated with the intellectual property. However, if we fail to prosecute the licensed patents, DRC has no contractual right to recover payments it has already made. Therefore this criterion is met.

- The seller's price to the buyer is fixed or determinable— As stated in section 1.2(a) of our DRC agreement, "DRC shall pay to Isis an aggregate purchase price (the "Purchase Price") of up to twenty-four million US dollars" and the Purchase Price is not subject to adjustment. Accordingly, the price is known and fixed; therefore, this criterion is met.

- Collectibility is reasonably assured—We recognize revenue when the cash has been received. Therefore collectibility is not an issue and this criterion is met.

Since we have met all four of the criteria under the provisions of SAB 104, the immediate recognition of revenue is appropriate for the payments received.

In connection with our response to the Staff's comments, we acknowledge the following:

- We are responsible for the adequacy and accuracy of the disclosure in our filings;

- Staff comments or changes to disclosure in response to Staff comments do not foreclose the Commission from taking any action with respect to the filing; and

- We may not assert Staff comments as a defense in any proceeding initiated by the Commission or any person under the federal securities laws of the United States.

Should you have any questions regarding our responses or require any additional information, please contact Elizabeth Hougen, Vice President, Finance and Chief Accounting Officer, at (760) 603-2492 or me at (760) 603-2460.

Sincerely,

/s/ B. Lynne Parshall

B. Lynne Parshall
Executive Vice President and Chief Financial Officer

ATTACHMENT A

Critical Accounting Policies

We prepare our consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. Each quarter, our senior management discusses the development, selection and disclosure of such estimates with the audit committee of our Board of Directors. There are specific risks associated with these critical accounting policies that we describe in the following paragraphs. For all of these policies, we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment. **Historically, our estimates have been accurate as we have not experienced any material differences between our estimates and our actual results.** The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessment of propriety of revenue recognition and associated deferred revenue;
- Determination of proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of proper valuation of inventory;
- Determination of appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of the appropriateness of judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine the fair value of stock-based compensation, including the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We follow the provisions as set forth by current accounting rules, which primarily include Staff Accounting Bulletin No. 101, or SAB 101, "*Revenue Recognition in Financial Statements,*" SAB 104, "*Revenue Recognition,*" and Financial Accounting Standards Board Emerging Issues Task Force No. 00-21, or EITF 00-21, "*Accounting for Revenue Arrangements with Multiple Deliverables*."

We generally recognize revenue when we have satisfied all contractual obligations and we are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue under current accounting rules. In those instances where we have billed our customers or received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on the balance sheet.

We often enter into collaborations where we receive non-refundable upfront payments for prior or future expenditures. We recognize revenue related to upfront payments ratably over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligations when the agreements we enter into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. **To date our estimates have not required material adjustments.** We have made estimates of our continuing obligations on several agreements, including our collaborations with Antisense Therapeutics Ltd., Lilly, OncoGenex and Pfizer. **Our collaborative agreements typically include a research and/or development project plan that includes activities to be performed in the collaboration and the party responsible for performing them. We estimate the period of time over which we will complete the activities for which we are responsible and use that period of time as our period of performance for purposes of revenue recognition and amortize revenue over such period. When our collaborators have asked us to continue performing work in a collaboration beyond the initial period of performance, we have extended our amortization period to correspond to the new extended period of performance. In no case have adjustments to performance periods and related adjustments to revenue amortization periods had a material impact on our revenue.**

Our collaborations often include contractual milestones. When we achieve these milestones, we are entitled to payment, as defined by the underlying agreements. We generally recognize revenue related to milestone payments upon completion of the milestone's performance requirement, as long as we are reasonably assured of collecting the resulting receivable and we are not obligated for future performance related to the achievement of the milestone. To date, we have earned milestone payments totaling $1.2 million under our Pfizer collaboration. Additionally, in January 2006, Lilly initiated clinical trials of LY2275796 for which we received a $750,000 milestone payment and Merck initiated clinical trials of a drug for HCV for which we earned a $1 million milestone payment.

We generally recognize revenue related to the sale of our drug inventory as we ship or deliver drugs to our partners. In several instances, we completed the manufacturing of drugs, but our partners asked us to deliver the drug on a later date. Under these circumstances, we ensured that our obligation was complete under the terms of the manufacturing agreement in place and title had transferred to the customer before we recognized the related revenue.

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. We generally recognize as revenue immediately those licensing fees and royalties for which

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we have no future performance obligations and are reasonably assured of collecting the resulting receivable. In the third quarter of 2006, we earned licensing revenue of $750,000 from Alnylam as a result of Alnylam's alliance with a pharmaceutical company for the development of RNA interference therapeutics. In addition, in October 2006, in accordance with contractually determined timing, we received an $8 million payment from Drug Royalty USA, Inc. as partial payment for the monetization of our royalty rights in Macugen.

We often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

In the fourth quarter of 2006, we sold our first commercial Ibis T5000 Biosensor System. The sale of an Ibis T5000 Biosensor System contains multiple elements. Since we have no previous experience of commercially selling the Ibis T5000 Biosensor System, we have no basis to determine the fair values of the various elements included in the system; therefore, we must account for the entire system as one deliverable and recognize revenue over the entire period of performance. For a one-year period following

the sale, we have ongoing support obligations for the Ibis T5000 Biosensor System, therefore we are amortizing the revenue for the entire system over a one-year period. Once we obtain a sufficient number of sales to enable us to identify each element's fair value, we will be able to recognize revenue separately for each element.

As part of our Lilly alliance, in 2001 Lilly provided us a $100.0 million interest free loan to fund the companies' research collaboration. We took quarterly draw downs against this loan and discounted the amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to us to help fund the research collaboration. We accounted for this difference as deferred revenue and recognized it as revenue over the period of contractual performance. In August 2005, we converted the loan into 2.5 million shares of our common stock. Concurrent with the conversion, we extended the research collaboration.

Valuation of Investments in Marketable Securities

We account for our investments in marketable securities in accordance with current accounting rules as set forth by SFAS 115, "*Accounting for Certain Investments in Debt and Equity Securities.*" We carry these investments at fair market value based upon market prices quoted on the last day of the fiscal quarter. We record unrealized gains and losses as a separate component of stockholders' equity, and include gross realized gains and losses in investment income.

In addition to our investments in marketable securities, we have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is other-than-

temporary, we examine historical trends in the stock price, the financial condition of the issuer, near term prospects of the issuer, and our current need for cash. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During the second quarter of 2006, we recorded a net gain on investments. This net gain on investments represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we own, partially offset by a non-cash loss on investment of $465,000 related to the impairment of our equity investment in ATL, which we believe was primarily a result of the financial market conditions related to biotechnology companies at that time. In the second half of 2006, we recorded a net unrealized gain of $390,000 related to our equity investment in ATL as a separate component of stockholders' equity. This reflected the increase in the market value of the investment since the impairment in the second quarter of 2006. We did not record an impairment loss on our investments in 2005. During 2004, we recorded a non-cash loss on investments of $5.1 million, principally related to the impairment of our equity investment in Alnylam.

Valuation of Long-Lived Assets

We assess the value of our long-lived assets, which include property and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, or SFAS 144. We evaluate our long-lived assets for impairment on at least a quarterly basis. During this process, we review our property and equipment listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties to determine if any impairment is present.

We consider the following factors:

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;
- Adverse changes in legal factors or in the business climate that would affect the value of an asset;
- An adverse action or assessment by a regulator;
- An accumulation of costs significantly in excess of amounts originally expected to acquire or construct an asset;

- Current period operating or cash flow loss combined with a history of operating or cash flow losses associated with an asset used for the purpose of producing revenue; and

- Challenges or potential challenges to our existing patents, the likelihood of applications being issued and the scope of our issued patents.

In December 2004, we made a strategic decision to focus our resources on our key programs. As a result, during the fourth quarter of 2004 we recorded charges of approximately $11.5 million related to the write-down of tangible and intangible assets, including equipment and patent costs that were non-essential to our current focus. We had additional write-downs of $15.6 million in 2005 associated with our restructuring

activities, which were primarily related to the sale of three of our buildings. In 2006, we incurred charges of $2.4 million primarily related to the write-down of equipment and patent costs that were non-essential to our current focus.

Valuation of Inventory

In accordance with SFAS 2, *Accounting for Research and Development Costs*, we capitalize the costs of raw materials that we purchase for use in producing our drugs because, until we use these raw materials, they have alternative future uses. We include in inventory raw material costs and related manufacturing costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. **Each of our raw materials can be used in multiple products and, as a result, have future economic value independent of the development status of any single drug. For example, if one of our drugs failed, the raw materials allocated for that drug have economic value for other drugs that we manufacture.** We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. Also included in inventory, as of December 31, 2006, are material costs and related manufacturing costs associated with our Ibis T5000 Biosensor System. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. In the fourth quarter of 2004, we recorded a charge of approximately $21.0 million for the write-down of inventory to its net realizable value related to our decision to focus our resources on key programs.

Estimated Liability for Clinical Development Costs

We record accrued liabilities related to unbilled expenses for which service providers have not yet billed us related to products or services that we have received, specifically related to ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory and analysis costs, toxicology studies and investigator grants. We have multiple drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. In order to ensure that we have adequately provided for ongoing preclinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these expenses. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. Upon settlement, these costs may differ materially from the amounts accrued in our consolidated financial statements. **Our historical accrual estimates have not been materially different from our actual amounts.**

Valuation Allowance for Net Deferred Tax Assets

We record a valuation allowance to offset our net deferred tax assets because we are uncertain that we will realize these net tax assets. We have had net operating losses since inception, and as a result, we have established a 100% valuation allowance for our

net deferred tax asset. When and if circumstances warrant, we will assess the likelihood

that our net deferred tax assets will more likely than not be recovered from future taxable income and record an appropriate reversal to the valuation allowance.

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our Ibis Biosciences, Inc. subsidiary based on the segregation of revenues and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. **We have not made material changes to our allocation methodologies since we began reporting segment financial information and results.** Different assumptions or allocation methods could result in materially different results by segment.

Stock-Based Compensation

On January 1, 2006, we adopted SFAS 123R, *Share-Based Payment*, which requires the measurement and recognition of compensation expense for all stock-based payment awards made to employees and directors including employee stock options and employee stock purchases related to our Employee Stock Purchase Plan based on estimated fair values. SFAS 123R supersedes our previous accounting under APB 25, *Accounting for Stock Issued to Employees* and SFAS 123, *Accounting for Stock-Based Compensation*, beginning January 1, 2006. In March 2005, the SEC issued SAB 107 relating to SFAS 123R. We have applied the provisions of SAB 107 in our adoption of SFAS 123R.

We adopted SFAS 123R using the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of our fiscal year 2006. Our Consolidated Statements of Operations for the year ended December 31, 2006 reflect the impact of SFAS 123R. In accordance with the modified prospective transition method, our Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact of SFAS 123R. As of December 31, 2006, there was $6.3 million of total unrecognized compensation cost related to non-vested stock-based compensation plans. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.2 years.

We utilize the Black-Scholes model and assumptions discussed in Note 4 for estimating the fair value of the stock-based awards we granted. Compensation expense for all stock-based payment awards is recognized using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. Our risk-free interest rate assumption is based upon observed interest rates appropriate for the term of our employee stock options and our ESPP. The dividend yield assumption is based on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use a weighted

average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model consistent with SFAS 123R. The expected term of stock options granted represents the period of time that they are expected to be outstanding. For our 2002 Non-Employee Directors' Stock Option Plan, we estimate the expected term of options granted based on historical exercise patterns. For our employee stock option plans, the estimated expected term is a derived output of the simplified method, as allowed under SAB 107. We estimated forfeitures based on historical experience. **There were no material changes to our estimated forfeitures in fiscal 2006.** For the periods prior to fiscal 2006, we accounted for forfeitures as they occurred in our pro forma information as required under SFAS 123.

ATTACHMENT B

Collaborative Arrangements and Licensing Agreements

Antisense Drug Discovery Collaborations

Pfizer, Inc.

In May 2005, Isis entered into a multi-year drug discovery collaboration with Pfizer to identify second generation antisense drugs for the treatment of ophthalmic disease. **Under the terms of the agreement, Isis received an upfront technology access fee of $1.0 million and amortized this amount over the one year period of Isis' performance based on the research plan included in the agreement, which ended in April 2006. There were no changes in Isis' period of performance. The amount of deferred revenue was $0 and $333,000 at December 31, 2006 and 2005, respectively.** To date, Isis has earned milestone payments totaling $1.2 million under the collaboration. Pfizer will also pay Isis additional milestone payments if key research, clinical, regulatory and sales milestones are achieved, and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug for the first indication, Isis will earn milestone payments totaling up to $26.1 million. In addition, Isis will receive royalties on the sale of drugs resulting from the collaboration. **For the years ended December 31, 2006, 2005 and 2004, Isis recognized revenue of $408,000, $2.2 million and $0, respectively, related to this collaboration.**

Eli Lilly and Company

In August 2001, Isis entered into a broad strategic relationship with Lilly, which included a joint antisense research collaboration in the areas of cancer, metabolic and imflammatory diseases and a $100 million loan that Lilly provided to Isis to fund its obligations under the research collaboration.

In August 2005, Isis extended the research collaboration with Lilly for approximately 24 months to focus on a select number of targets. During the extension, Isis and Lilly will continue to advance antisense drugs identified during the initial collaboration, and continue their efforts to develop and refine antisense technologies. During the extension, Isis is using collaboration funds to support its scientists and Lilly is supporting Lilly scientists. The extended collaboration provides Lilly access to Isis' patents to support Lilly's internal antisense drug discovery and development program for a limited number of targets. As part of the extension, Isis and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using advanced generation chemistries. In connection with the extension, Isis converted the $100 million loan that Lilly previously provided to it into 2.5 million shares of Isis common stock.

As part of the collaboration, Lilly licensed LY2181308, Isis' antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eIF-4E. *To date, Isis has earned $4.1 million and $1.5 million in license fees and milestone payments related to the continued development of LY2181308 and LY2275796, respectively.* **Isis amortized the $1.1 million license fee related to LY2181308 over a two-year period, which ended in June 2004. The two-year period corresponded to Isis' period of performance for**

LY2181308 and there were no changes to the period of performance. In September 2004, Isis recognized $750,000 associated with the license fee it received for LY2275796. Lilly is responsible for the preclinical and clinical development of LY2275796 and Isis has no performance obligations for this drug. Isis will receive additional milestone payments aggregating up to $25.0 million and $19.5 million if LY2181308 and LY2275796, respectively, achieve specified regulatory and commercial milestones, and royalties on future product sales of these drugs.

As part of the collaboration extension, Isis is exploring with Lilly antisense drugs targeting Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. Isis is working closely with Lilly to advance an improved STAT-3 candidate into development.

Isis' relationship with Lilly historically provided several revenue sources, including research funding related to the $100 million research loan and development milestones similar to the milestones for LY2181308 and LY2275796. *During 2006, 2005, and 2004, Isis generated revenue from its relationship with Lilly totaling $1.2 million, $10.8 million, and $15.7 million, respectively, which comprised 5%, 27%, and 37%, respectively, of Isis' total revenue during those same periods.*

Satellite Company Drug Discovery and Development Collaborations

Antisense Therapeutics Limited

In December 2001, Isis licensed ATL1102 to ATL, an Australian company publicly-traded on the Australian Stock Exchange. Isis was responsible for completing the required preclinical studies for ATL1102 and for manufacturing the drug for human clinical trials at ATL's expense. ATL agreed to undertake the future clinical development and commercialization of the drug.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and site disorders. ATL1103 is a product of Isis' joint antisense drug discovery and development collaboration, which Isis recently extended for an additional two years. ATL pays Isis for access to its antisense expertise and for research and manufacturing services Isis may provide to ATL during the collaboration. Additionally, ATL will pay Isis royalties on any antisense drugs discovered and developed within the partnership.

In connection with this collaboration, Isis received 30.0 million shares of ATL common stock upon completion of ATL's initial public offering ("IPO"), representing an initial ownership percentage of approximately 14%, and options to purchase an additional 20.0 million shares of ATL common stock, which expired in 2006. **The initial ATL common stock Isis received had a value of $2.8 million, and Isis recognized this amount into revenue ratably over the five-year period of performance under the collaboration, which ended in November 2006. There were no changes in Isis' period of performance. The amount of deferred revenue was $0 and $506,000 at December 31, 2006 and 2005, respectively.** *For the years ended December 31, 2006, 2005, and 2004, Isis recorded revenue of $652,000, $698,000, and $1.4 million, respectively, related to this collaboration.* As of December 31, 2006, Isis' ownership percentage in ATL, including 10.3 million shares Isis purchased subsequent to shares it acquired in the IPO, was less than 10%. Isis' balance sheets at December 31, 2006 and

2005 included a short-term investment at fair market value of $1.3 million and $1.2 million, respectively, related to this equity investment.

OncoGenex Technologies Inc.

In November 2001, Isis established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug resistant and metastatic cancers, to co-develop and commercialize OGX-011, an anti-cancer antisense drug. Isis funds 35% of the costs of developing OGX-011. In exchange, Isis receives 35% of any revenue generated by OncoGenex for OGX-011. OGX-011 combines OncoGenex's proprietary antisense position in inhibitors to the target clusterin, with Isis' proprietary second generation antisense chemistry. Isis conducted preclinical toxicology and pharmacokinetic studies of OGX-011 during 2002. Isis also manufactured OGX-011 for preclinical and Phase 1/2 studies. OncoGenex's Phase 1 clinical trials to assess the safety of OGX-011 in combination with hormone ablation therapy in men with localized prostate cancer and in combination with standard chemotherapy in patients with solid tumors known to express clusterin formed the basis for OncoGenex's broad Phase 2 program for OGX-011. OncoGenex currently has five ongoing Phase 2 studies of OGX-011 for the treatment of prostate, non-small cell lung and breast cancers.

In September 2003, the companies expanded their antisense drug development partnership to include the development of the second generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for the preclinical and clinical development of the drug **and Isis has no performance obligations**. *OncoGenex issued to Isis* **$750,000 of** *OncoGenex securities as payment for an upfront fee.* In addition, OncoGenex will pay Isis milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and pay Isis royalties on product sales. As of December 31, 2006, OncoGenex had not triggered any of these milestone payments related to OGX-225.

In January 2005, Isis further broadened its antisense drug development partnership with OncoGenex to allow for the development of two additional second generation antisense anti-cancer drugs. Under the terms of the agreement, OncoGenex is responsible for the preclinical and clinical development of the drugs **and Isis has no performance obligations**. In April 2005, OncoGenex selected its first drug under this expansion, OGX-427. OGX-427 targets heat shock protein 27, or Hsp27, which is over-expressed in numerous tumor types and is associated with treatment resistance through its ability to help cancer cells survive stress-induced injury. *OncoGenex paid Isis an upfront fee* **of $750,000** *with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock.* OncoGenex will also pay Isis milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs. **As of December 31, 2006,**

OncoGenex had not met any of the milestones that would result in payments related to OGX-427.

For the years ended December 31, 2006, 2005 and 2004, Isis earned revenue of $1.2 million, $2.7 million and $669,000, respectively, related to its collaboration with OncoGenex. Isis' balance sheets at December 31, 2006 and 2005 include a long-term

investment of $1.5 million related to Isis' equity investment in OncoGenex. While there is no readily determinable market value for these securities, there has been no indication that Isis' investment in OncoGenex has been impaired; accordingly, Isis believes that the carrying value of this investment is equal to or below its current fair market value.

ATTACHMENT C

In April 2006, Isis granted the members of Symphony GenIsis Holdings LLC warrants to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share. **These warrants expire on April 7, 2011 and can be settled with unregistered shares of Isis' common stock.** At December 31, 2006, all of these warrants remained issued and outstanding. If Isis enters into a merger or acquisition in which the surviving or resulting "parent" entity is an entity other than Isis, then the holders of these warrants may exchange the warrants for a new warrant exercisable in return for shares of common stock of the surviving entity as follows:

- if the terms of such merger or acquisition provide for consideration that consists solely of stock of the surviving entity, and the surviving entity has a class of common stock traded on a major national exchange or foreign exchange ("Public Common Shares"), then any replacement warrants issued to the holders will be solely for such publicly traded common shares, at an exchange ratio reflecting the stock consideration paid at the time of such change in control; or

- if the terms of such merger or acquisition shall provide for consideration that consists of cash or a combination of cash and Public Common Shares of the surviving entity, then any replacement warrants issued to the holders will be solely for Public Common Shares of the surviving entity, at an exchange ratio reflecting the total consideration paid by the surviving entity at the time of such change in control, as if the total consideration (including cash) for each share of Isis' common stock was instead paid only in Public Common Shares of the surviving entity at the time of such change of control; or

- if the surviving entity is a private corporation, closely held company or other entity that does not have a class of Public Common Shares, then the holders of the warrants may elect to surrender all outstanding warrants to Isis in consideration of a cash payment for each share of its common stock subject to purchase under the warrants in an amount equal to 40% of the per share cash consideration to be received by a holder of one share of its common stock to be tendered in the merger or acquisition, subject to an aggregate limit of $22,000,000.

In connection with the issuance of the warrants, Isis entered into a registration rights agreement with Symphony GenIsis Holdings LLC. Pursuant to the registration rights agreement, Isis filed a registration statement with the SEC covering the shares of common stock issuable upon exercise of the warrants. Isis is required to use commercially reasonable efforts to maintain the effectiveness of the registration statement over the term of the warrant.

Isis evaluated the provisions of the registration rights agreement and the warrant purchase agreement under EITF 00-19, *Accounting for Derivative Financial*

***Instruments Indexed to, and Potentially Settled in, a Company's Own Stock,* and determined that the criteria for equity classification were met; therefore, the warrants were accounted for as part of stockholders' equity.**