UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

x **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the Quarterly Period Ended March 31, 2004

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporation or organization)	(IRS Employer Identification No.)

2292 Faraday Ave., Carlsbad, CA 92008
(Address of principal executive offices, including zip code)

760-931-9200
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: **None**
Securities registered pursuant to Section 12(g) of the Act:
Common Stock, $.001 Par Value

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No o

Indicate by check mark whether the registrant is an accelerated filer (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes ☒ No o

The number of shares of voting common stock outstanding as of May 5, 2004 was 56,025,849.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

INDEX

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED BALANCE SHEETS
(in thousands, except share data)

	March 31, 2004 (Unaudited)	December 31, 2003 (Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 39,757	$ 33,117
Short-term investments	141,116	182,387
Contracts receivable	5,774	2,657
Inventory	14,548	13,995
Other current assets	7,686	7,405
Total current assets	208,881	239,561
Property, plant and equipment, net	32,721	34,790
Licenses, net	27,782	28,363
Patents, net	23,556	22,374
Deposits and other assets	8,411	8,479
Long-term investments	11,375	1,375
Total assets	$ 312,726	$ 334,942
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,349	$ 3,720
Accrued compensation	2,058	4,149
Accrued liabilities	8,049	6,527
Current portion of long-term obligations	10,355	16,477
Current portion of deferred contract revenue	15,832	14,684
Total current liabilities	39,643	45,557
$5^1/_2$% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	94,558	88,397
Long-term deferred contract revenue, less current portion	5,971	8,810
Stockholders' equity:		
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value; 16,620 shares authorized, 12,015 shares issued and outstanding at March 31, 2004 and December 31, 2003	12,015	12,015
Accretion of Series B Preferred stock dividends	2,741	2,560
Common stock, $.001 par value; 100,000,000 shares authorized, 55,995,246 shares and 55,557,253 shares	56	56

issued and outstanding at March 31, 2004 and December 31, 2003, respectively		
Additional paid-in capital	610,517	604,948
Deferred compensation	(453)	(294)
Accumulated other comprehensive income	4,747	3,476
Accumulated deficit	(582,069)	(555,583)
Total stockholders' equity	47,554	67,178
Total liabilities and stockholders' equity	$ 312,726	$ 334,942

Note: The balance sheet at December 31, 2003 has been derived from the audited consolidated financial statements at that date.

See accompanying notes

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except for per share amounts)
(Unaudited)

	Three Months Ended March 31,	
	2004	2003
Revenue:		
Research and development revenue under collaborative agreements	$ 6,998	$ 13,780
Licensing and royalty revenue	5,305	200
Total revenue	12,303	13,980
Operating expenses:		
Research and development	28,947	30,261
General and administrative	2,453	2,622
Compensation expense related to stock options	3,238	9
Total operating expenses	34,638	32,892
Loss from operations	(22,335)	(18,912)
Other income (expenses):		
Investment income	1,133	1,636
Interest expense	(5,104)	(4,608)
Loss on investments	—	(2,438)
Net loss	(26,306)	(24,322)
Accretion of dividends on preferred stock	(181)	(171)
Net loss applicable to common stock	$ (26,487)	$ (24,493)
Basic and diluted net loss per share	$ (0.47)	$ (0.44)
Shares used in computing basic and diluted net loss per share	55,858	55,375

See accompanying notes

ISIS PHARMACEUTICALS, INC.
CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)
(Unaudited)

	Three Months Ended March 31,	
	2004	2003
Net cash used in operating activities	$ (23,467)	$ (18,005)
Investing activities:		
Purchase of short-term investments	(23,182)	(73,371)
Proceeds from the sale of short-term investments	64,181	52,412
Purchase of property, plant and equipment	(103)	(3,554)
Other assets	(1,837)	(1,365)
Strategic investments	(10,000)	—
Investments in affiliates	—	(5,193)
Net cash provided by (used in) investing activities	29,059	(31,071)

Financing activities:		
Net proceeds from issuance of equity	2,172	902
Proceeds from long-term borrowings	7,574	9,524
Principal payments on debt and capital lease obligations	(8,698)	(2,114)
Net cash provided from financing activities	1,048	8,312
Net increase (decrease) in cash and cash equivalents	6,640	(40,764)
Cash and cash equivalents at beginning of period	33,117	101,856
Cash and cash equivalents at end of period	$ 39,757	$ 61,092
Supplemental disclosures of cash flow information:		
Interest paid	$ 570	$ 273

See accompanying notes

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
March 31, 2004
(Unaudited)

1. Basis of Presentation

The unaudited interim consolidated financial statements for the three-month periods ended March 31, 2004 and 2003 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2003. The financial statements include all adjustments (consisting only of normal recurring adjustments), which Isis considers necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2003 included in Isis' Annual Report on Form 10-K filed with the Securities and Exchange Commission.

The condensed consolidated financial statements include the accounts of Isis and its wholly-owned subsidiary, Isis Pharmaceuticals Singapore Pte Ltd., established during October 2003. There were no current operations or results of operations for the wholly-owned subsidiary for the three months ended March 31, 2004.

2. Significant Accounting Policies

Revenue recognition

Isis ("the Company") recognizes revenue when it has satisfied all contractual obligations and Isis is reasonably certain it can collect the receivable.

Research and development revenue under collaborative agreements

Isis recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. Isis defers payments received under these agreements that relate to future performance and records revenue as earned over the specified future performance period. The Company recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as it satisfies its performance obligations. Isis recognizes revenue that relates to milestones upon completion of the milestone's performance requirement, and recognizes revenue from arrangements containing multiple deliverables in accordance with *Emerging Issues Task Force Issue No. 00-21* ("EITF 00-21"), *Accounting for Revenue Arrangements with Multiple Deliverables*. In these cases, the Company recognizes revenue from each element of the arrangement as long as it can determine a separate value for each element, it has completed its obligation to deliver or perform on that element, and is reasonably assured of collecting the resulting receivable. Isis records revenue from federal research grants and contracts during the period in which it incurs the related expenditures. Isis recognizes revenue from product sales as it ships the products.

Isis has implemented the provisions of Staff Accounting Bulletin No. 104 ("SAB 104"), which was issued in December 2003. SAB 104 updates portions of the interpretive guidance included in Topic 13 of the codification of Staff Accounting Bulletin No. 101 in order to make this interpretive guidance consistent with current authoritative accounting and auditing guidance and SEC rules and regulations. SAB 104 provides interpretation on selected revenue recognition issues. Under SAB 104, revenue should be recognized when it is realized or realizable and earned, and has met the following criteria: 1) persuasive evidence of an arrangement exists, 2) delivery occurred or services were rendered, 3) the seller's price to the buyer is fixed or determinable and 4) collectibility is reasonably assured. This statement has not had a material impact on the Company's operating results and financial position.

As part of Isis' alliance with Eli Lilly and Company ("Lilly") in August 2001, Lilly provided Isis a $100.0 million interest free loan to fund the research collaboration. As of March 31, 2004, Isis had drawn down $80.0 million on the $100.0 million loan. Isis discounted the $80.0 million loan to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis accretes 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 represents value Lilly gave to Isis to help fund the research collaboration. Isis accounts for this value as deferred revenue and recognizes it as revenue over the period of performance.

Licensing and royalty revenue

Isis recognizes licensing and royalty revenue immediately, if collectibility is reasonably assured, for arrangements in which Isis is not required to provide services in the future.

Concentration of credit risk

Financial instruments that potentially subject Isis to concentrations of credit risk consist primarily of cash equivalents, short-term investments and receivables. Isis places its cash equivalents and certain of its short-term investments with high credit-quality financial institutions. Isis invests its excess cash primarily in auction and money market instruments, and municipal and floating rate bonds. Isis and its audit committee established guidelines relative to credit ratings, diversification and maturities that seek to maintain safety and liquidity.

Cash, cash equivalents and short-term investments

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Isis' short-term investments have initial maturities of greater than ninety days from date of purchase. Isis classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* Isis carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal quarter. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses in investment income and these amounts have not been material. During the first quarter of 2003, Isis recorded a non-cash loss of $2.4 million related to the impairment of its equity investments in Antisense Therapeutics Limited ("ATL") and Hybridon, Inc. ("Hybridon"). This charge reflected the then-current market climate and was associated with the decline in market value of the equity investments from their initial valuations and Isis determined the decline in value to be other-than-temporary. Isis determined that there were no other-than-temporary declines in value for these investments during the three months ended March 31, 2004.

Inventory valuation

Isis' inventory includes drugs with alternative uses that are used primarily for its clinical development activities and drug products it manufactures for its partners under contractual terms. Isis states its inventory at the lower of cost or market, with cost determined under the first-in, first-out method. Isis reviews inventory periodically and reduces the carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. In the second quarter of 2003, Isis reduced the carrying value of its raw materials related to Affinitak to zero.

Inventory includes the following categories as of March 31, 2004 and December 31, 2003 (net realizable value in thousands):

	March 31, 2004	December 31, 2003
Raw materials	$ 1,695	$ 1,526
Work in process	10,799	9,920
Finished goods	2,054	2,549
	$ 14,548	$ 13,995

The composition of inventory among raw materials, work-in-process and finished goods fluctuates from period-to-period based on the nature and timing of Isis' manufacturing activities in response to product requirements to support clinical trials and partner collaborations.

Licenses

Isis obtains licenses from third parties and capitalizes the cost related to exclusive licenses. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between nine years and 15 years.

Patents

Isis capitalizes costs consisting principally of outside legal costs and filing fees related to obtaining patents. Isis reviews costs regularly to determine that they include costs for patent applications Isis is pursuing. Isis evaluates costs related to patents that Isis is not actively pursuing for impairment and writes off the related costs, if appropriate. Isis amortizes patent costs over their estimated useful lives of 10 years, beginning with the date the patents are issued.

Fair value of financial instruments

Isis has determined the estimated fair value of its financial instruments. The amounts reported for cash, accounts receivable, accounts payable and accrued expenses approximate the fair value because of their short maturities. Isis reports its investment securities at their estimated fair value based on quoted market prices of comparable instruments.

Long-lived assets

Pursuant to the provisions of SFAS 144, *Accounting for the Impairment of Long-Lived Assets*, Isis periodically evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, when events and circumstances indicate that these assets may be impaired.

Use of estimates

The preparation of consolidated financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Stock-based compensation

In April 2003, Isis implemented an employee stock option exchange program ("2003 option exchange program") to maintain one of Isis' key assets, its employee base, in a manner that was sensitive to shareholder interests. The 2003 option exchange program allowed employees during the offering period, which began on April 8, 2003 and ended on May 8, 2003, to surrender options, granted prior to January 5, 2002, which had higher exercise prices, in exchange for a lesser number of options, which had lower exercise prices. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1.0 million options having an exercise price of $5.15. The new options vest over three years beginning on January 1, 2003 and expire on December 31, 2008. Isis accounts for the affected options using variable accounting consistent with the provisions of APB 25 and FIN 44, and will continue to account for the affected options using variable accounting until all these options have been exercised or cancelled. As a result, Isis recorded compensation expense of approximately $3.2 million during the three months ended March 31, 2004.

Isis has adopted the disclosure-only provision of SFAS 123, *Accounting for Stock-Based Compensation* ("SFAS 123"). Accordingly, Isis has not recognized compensation expense, except primarily for compensation expense related to the affected options from the 2000 and 2003 option exchange programs, for the Isis stock option plans. Had Isis determined compensation expense consistent with SFAS 123, Isis would have reported the following proforma amounts for net loss and basic and diluted net loss per share (in thousands, except per share amounts):

	Three Months Ended March 31,	
	2004	2003
Net loss applicable to common stock—as reported	$ (26,487)	$ (24,493)
Net loss applicable to common stock—pro forma	$ (25,100)	$ (27,521)
Basic and diluted net loss per share—as reported	$ (0.47)	$ (0.44)
Basic and diluted net loss per share—pro forma	$ (0.45)	$ (0.50)

For purposes of proforma disclosures, Isis estimated the fair value of each option grant on the date of grant using the Black-Scholes option pricing model with the following weighted-average assumptions:

	March 31,	
	2004	2003
Risk-free interest rate	3.8%	3.8%
Dividend yield	0%	0%
Volatility	74.6%	82.1%
Expected Life	6.23 years	5.5 years

The weighted average fair value of options granted were $6.91 and $6.72 for the three months ended March 31, 2004 and 2003, respectively.

Comprehensive income

SFAS No. 130, *Reporting Comprehensive Income*, requires Isis to report, in addition to net loss, comprehensive loss and its components. A summary follows (in thousands):

	Three Months Ended March 31,	
	2004	2003
Comprehensive loss:		
Change in unrealized gains (losses)	$ 1,271	$ 2,210
Net loss applicable to common stock	(26,487)	(24,493)
Comprehensive loss	$ (25,216)	$ (22,283)

Impact of recently issued accounting standards

In March 2004, the FASB issued EITF 03-06, *Participating Securities and the Two-Class Method under FASB Statement No. 128, Earnings per Share.* EITF 03-06 provides guidance in determining when a security participates in dividends such that the two-class method must be used to calculate earnings per share. Under FASB No. 128, the two-class method results in an allocation of all undistributed earnings to common shares and other participating securities as if all those earnings were distributed, which can result in a substantial reduction in both basic and diluted earnings per share attributable to the common stock. EITF 03-06 will be effective for the quarter beginning April 1, 2004. Isis does not expect that the adoption of EITF 03-06 will have a material impact on its earnings per share presentation.

In March 2004, the FASB issued EITF 03-01, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments.* EITF 03-01 requires a three-step model to determine other-than-temporary impairments for all current and future investments in marketable securities, and will be effective for interim and annual reporting periods beginning after June 15, 2004. Isis does not expect that the adoption of EITF 03-01 will have a material impact on its operating results and financial position.

In January 2003, the FASB issued FASB Interpretation No. 46 ("FIN 46"), *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51*, which addresses consolidation by business enterprises of variable interest entities ("VIE"s) either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. In December 2003, the FASB completed deliberations of proposed modifications to FIN 46 ("Revised Interpretations") resulting in multiple effective dates based on the nature as well as the creation date of the VIE. Isis has applied the Revised Interpretations for the quarter ended March 31, 2004. As of March 31, 2004, Isis had a collaborative arrangement with a development stage biopharmaceutical company (the

"investee") developing drugs based on RNA splicing technology. Isis considers this entity to be a VIE under the provisions of FIN 46. During 2003 and early 2004, Isis advanced initial funding of $500,000 and $250,000, respectively, in cash in exchange for a convertible promissory note, which will convert into securities that the investee issues in its next round of equity financing. To date, Isis has contributed the substantial portion of this entity's funding. Due to the uncertainty in ultimately realizing any value from the consideration paid, Isis expensed the payments when made. In addition, since Isis did not hold equity ownership in the investee as of March 31, 2004, Isis was not

required to consolidate the investee's results of operations under FIN 46. Based upon these factors, the adoption of FIN 46 did not have a material impact on Isis' operating results and financial position for the three months ended March 31, 2004.

3. Strategic Alliances

Science Applications International Corporation

In March 2004, Isis entered into a two-year contract with Science Applications International Corporation ("SAIC") to further the development of Isis' TIGER biosensor to identify infectious agents in biological warfare attacks. The contract provides for up to $19.5 million in funding by the Defense Advanced Research Projects Agency ("DARPA").

Alnylam Pharmaceuticals, Inc.

In March 2004, Isis entered into a strategic alliance with Alnylam Pharmaceuticals, Inc. ("Alnylam") to develop and commercialize RNAi therapeutics. Under the terms of the agreement, Isis exclusively licensed to Alnylam its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5.0 million license fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments. In turn, Alnylam nonexclusively licensed Isis its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for single-stranded RNAi therapeutics and to a limited extent for double-stranded RNAi therapeutics. If Isis develops or commercializes an RNAi based drug using Alnylam's technology, Isis will pay Alnylam milestones and royalties.

Isis recorded $5.0 million in licensing revenue from this strategic alliance during the three months ended March 31, 2004. As of March 31, 2004, Alnylam had paid $3.0 million of this fee to Isis. The remaining $2.0 million is due and payable to Isis within the next 12 months and is reflected in contracts receivable on the accompanying condensed consolidated balance sheet as of March 31, 2004.

As part of the agreement, Isis also made a $10.0 million equity investment in Alnylam.

4. Affiliates

Orasense

Due to the significant minority investor rights retained by Elan and its subsidiaries, Isis accounted for its investment in Orasense under the equity method of accounting. Through December 2002, Orasense incurred research and development expenses, performed by Elan and Isis on Orasense's behalf, in the course of its product development. In conjunction with its continuing restructuring efforts, Elan concluded its participation in the Orasense collaboration effective December 31, 2002. As a result, Isis regained all rights to ISIS 104838, the compound that Elan and Isis were developing within Orasense. Isis has continued to develop its oral delivery technology within Orasense. The following table presents summary results of operations for the three months ended March 31, 2004 and 2003 for Orasense (in thousands):

	Three Months Ended March 31,	
	2004	2003
Revenue	$ —	$ —
Research and development expense	539	916
Net loss	$ (539)	$ (916)

5. Significant Partners and Concentration of Business Risk

Isis does not generate sales from products but has historically funded its operations in part from collaborations with corporate partners and various government agencies. A relatively small number of partners historically have accounted for a significant percentage of Isis' revenue. During the three months ended March 31, 2004, three significant partners accounted for approximately 41%, 23% and 18% of revenue, respectively. During the three months ended March 31, 2003, two significant partners accounted for 68% and 12% of revenue, respectively. During the three months ended March 31, 2004 and 2003, Isis derived approximately 24% and 15%, respectively, of its revenue directly or indirectly from agencies of the U.S. Government. Contract receivables from a single partner comprised approximately 77% and 49% of contract receivables at March 31, 2004 and December 31, 2003, respectively.

6. Subsequent Event

In May 2004, Isis extended its antisense drug discovery collaboration in cancer with Lilly. During this extension, Isis and Lilly will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using second and third generation chemistries. Under the collaboration, Isis and Lilly will also explore potential new anticancer drug targets using RNA-directed technologies. The amendment extends this oncology relationship, initiated in June 2002, through the end of the research collaboration.

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

In addition to historical information contained in this Report on Form 10-Q, this Report contains forward-looking statements regarding our business and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of developing technology and systems used to identify infectious agents, in discovering and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this Report on Form 10-Q. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in our Annual Report on Form 10-K for the year ended December 31, 2003, which is on file with the U.S. Securities and Exchange Commission, and those identified in the section of Item 2 entitled "Risk Factors" beginning on page 20 of this Report. As a result, you should not rely on these forward-looking statements.

Overview

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We have designed antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding the capabilities of antisense drugs in treating disease. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and we have successfully turned our expertise into 11 antisense drugs currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including metabolic, cardiovascular, inflammatory and viral diseases, and cancer. We are studying these drugs in intravenous, subcutaneous, topical cream, enema, aerosol, and oral formulations, and we are advancing antisense drugs using second-generation chemistry. We achieved marketing clearance for the world's first antisense drug, Vitravene (fomivirsen) in 1998.

Affinitak, formerly LY900003 or ISIS 3521, which we licensed to Lilly in 2001, is our most advanced product in development. In March 2003, we announced the results of our Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer, which were not sufficient to support a single study new drug application. Lilly and we completed an analysis of the data from this trial and presented a summary of the findings at the 39th Annual Meeting of the American Society of Clinical Oncology in June 2003. In a second Phase III study, Lilly is continuing to follow enrolled patients. Lilly and we will make a decision about the future development of Affinitak pending a review upon completion of the second Phase III trial, which likely will occur in the second half of 2004.

We are conducting two Phase III clinical trials for another product, alicaforsen, or ISIS 2302, in an inflammatory bowel disease known as Crohn's disease. These trials are being conducted in North America, Europe, and Israel. We expect to report data from these clinical trials in the second half of 2004. We also have Phase II programs ongoing for five additional products.

Our Ibis program has invented a platform technology that has the potential to revolutionize the identification of infectious diseases. Through a project called Triangulation Identification for Genetic Evaluation of Risks, or TIGER, we have applied our proprietary technologies to develop a biological sensor to identify a broad range of infectious organisms in a sample, including organisms that are newly-emerging, genetically altered and unculturable. We have successfully demonstrated proof-of-principle of the TIGER biosensor with the identification of a variety of bacteria and viruses in both environmental and human clinical samples. To date, our Ibis program has received awards and contracts worth up to $55.0 million through our collaborations with agencies of the U.S. Government, including DARPA, the Centers for Disease Control, or CDC, the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID, the US Navy, and the Federal Bureau of Investigation, or FBI, among others.

We have a broad patent portfolio covering our technologies. We have rights to more than 1,300 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. To date, we have generated more than $40.0 million in license and royalty fees related to our patent portfolio.

The principal purpose of our intellectual property portfolio is to protect our inventions in RNA-based drug discovery. Our intellectual property estate also enables us to expand our pipeline by granting partners limited access to antisense technology, through licenses we grant them. Licensing partnerships may include antisense drug discovery collaborations like those we have with Lilly and Amgen, and functional genomics agreements, like our licenses to Chiron, Amgen, Sequitur and atugen AG. We also license our non-antisense patents, as we did to Eyetech Pharmaceuticals, Inc.

We are pursuing early-stage antisense mechanisms, including RNA Interference, or RNAi, micro-RNA, and alternative splicing through research collaborations and partnerships, like our strategic alliances with Alnylam, the Singapore Economic Development Board, or Singapore EDB, and Ercole Biotech, Inc.

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. We discuss the development, selection and disclosure of such estimates with our audit committee each quarter. 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 may periodically require adjustment. 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;
- 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; and
- Estimation of our net deferred income tax asset valuation allowance.

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 Emerging Issue 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. We include in deferred revenue on the

balance sheet any revenues which we are entitled to bill or have collected in advance of recognizing the associated revenue.

We often enter into collaborations where we receive nonrefundable up-front payments for prior or future expenditures. We recognize revenue related to up-front 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. We have made estimates of our continuing obligations on several agreements, including our collaborations with ATL, Amgen, Chiron, Lilly and the Singapore EDB.

As part of our Lilly alliance, in 2001 Lilly provided us a $100.0 million interest free loan to fund the research collaboration. We take quarterly drawdowns against this loan and discount 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. As of March 31, 2004, we had drawn down $80.0 million on this loan. We are accreting 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 represents value Lilly gave to us to help fund the research collaboration. We account for this difference as deferred revenue and recognize it as revenue over the period of contractual performance.

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 milestones 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 to future performance related to the achievement of the milestone. We generally recognize revenue related to the sale of our inventory as we ship or deliver drugs to our partners. To date, in two 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 and/or royalty fees. We generally recognize as revenue immediately those licensing and royalty fees for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable.

We sometimes 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.

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 also 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 first quarter of 2003, we recorded a non-cash loss of $2.4 million related to the impairment of our equity investments in ATL and Hybridon. We

recorded these charges based on declines in market value of the equity investments, as compared to their initial valuations, which we determined to be other-than-temporary.

Results of Operations

Revenue

Our total revenue for the three months ended March 31, 2004 was $12.3 million, compared to $14.0 million for the same period in 2003.

Under the category research and development revenue under collaborative agreements, we earned revenue of $7.0 million for the three months ended March 31, 2004, compared to $13.8 million for the same period in 2003. The decrease reflects a reduction in revenue associated with the completion of our Phase III trial of Affinitak™, offset in part by an increase in revenue associated with the continued development of our TIGER biosensor technology. Our ability to maintain revenue at current levels will depend on new revenue sources and expansion of existing revenue sources for the remainder of 2004.

Our revenue from licensing activities and royalties was $5.3 million for the three months ended March 31, 2004, compared with $200,000 for the same period in 2003. This increase reflects the $5.0 million license fee we earned under our strategic alliance with Alnylam.

Operating Expenses

Total operating expenses for the three months ended March 31, 2004 were $34.6 million, compared to $32.9 million for the same period in 2003. The increase of $1.7 million was primarily due to increased expenses of $3.2 million of non-cash compensation expense due to variable accounting for stock options, offset by decreases in research and development and general and administration expenses as we describe in the following paragraphs. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude compensation expense related to stock options from operating expenses because it is based on the variability of our stock price rather than operations.

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, our Ibis program, and R&D Support costs. For the three months ended March 31, 2004, we incurred total research and development expenses of $28.9 million, compared to $30.3 million for the same period in 2003. The decrease of $1.4 million was related to our implementation of an expense reduction plan during the second quarter of 2003 and the completion in 2003 of our Phase III trial of Affinitak. These decreases were partially offset by increased clinical development expenses for many of our other products and increased costs in our Ibis program related to the continued development of our TIGER biosensor technology.

Antisense drug discovery costs for the three months ended March 31, 2004 were $9.0 million, compared to $10.0 million for the same period in 2003. The decrease of $1.0 million was principally the result of our planned expense reductions, which began in the second quarter of 2003. We anticipate that our existing relationships and collaborations as well as prospective new partners, will continue to help fund our many research programs, as well as contribute to the advancement of the science by funding core antisense technology research.

Antisense drug development expenditures were $10.3 million for the three months ended March 31, 2004, compared to $12.1 million for the same period in 2003. The decrease of $1.8 million was primarily due to the completion in 2003 of our Phase III trial of Affinitak, offset by increased clinical development expenses for many of our other products. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials. We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the variety of indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Generally, a late stage Phase III trial is substantially more expensive than early stage trials,

such as Phase I or Phase II. Currently we have 11 drug candidates in various stages of development, including two drugs in Phase III clinical trials, Affinitak and alicaforsen for Crohn's disease.

Expenditures related to Affinitak for the three months ended March 31, 2004 were $42,000, compared to $2.9 million for the same period in 2003. The decrease was primarily due to a reduction in costs associated with the development of Affinitak following the disappointing results from the first Phase III trial of Affinitak and the decision not to file an NDA in 2003. Our partner, Lilly, is continuing to follow enrolled patients in a second Phase III trial for Affinitak. Lilly and we will make a decision about the future development of Affinitak pending a review upon completion of this second Phase III trial, which likely will occur in the second half of 2004.

We incurred development expenditures of $1.8 million for the three months ended March 31, 2004 and 2003 for our second drug in Phase III trials, alicaforsen for Crohn's disease. This is consistent with our ongoing development efforts for alicaforsen.

We incurred expenses related to our other products in development of $6.7 million for the three months ended March 31, 2004, compared to $4.9 million for the same period in 2003. The $1.8 million increase is primarily the result of an increase in development activity related to Phase I and Phase II trials for our ulcerative colitis, diabetes, cancer and cardiovascular drugs, as well as expenses related to products in the early stages of development.

Our Ibis program expenses for the three months ended March 31, 2004 were $3.1 million, compared to $2.6 million for the same period in 2003. The $500,000 increase was primarily related to our continued performance obligations under our multi-year government contracts with SAIC, USAMRIID, the CDC, and with various other government agencies. We include in Ibis expenses all contract-related costs we incur on behalf of government agencies in connection with the performance of our obligations under the respective contracts, including costs for equipment to which the government retains title. We expect our costs for Ibis to increase as we continue to expand this business.

R&D Support costs for the three months ended March 31, 2004 were $6.6 million, compared to $5.6 million for the same period in 2003. While we experienced decreases in direct research and development costs during the first three months of 2004 as compared to 2003 related to decreased costs for Affinitak and our cost reduction efforts, we did not experience similar reductions in R&D Support costs. A significant portion of R&D Support costs include fixed occupancy and facility costs, patent costs, and personnel costs that support the entire research and development organization. While we work to control our R&D Support costs, we expect that they will increase as we advance the clinical and preclinical development of our products. Specifically, we expect our depreciation and amortization expense to increase as we continue to make investments in capital equipment and patents to support our development activities.

General and administrative expenses for the three months ended March 31, 2004 were $2.5 million, compared to $2.6 million for the same period in 2003. The $100,000 decrease for the first quarter of 2004 over 2003 was primarily a result of a decrease in employees and related benefits compared to the first quarter of 2003. As a result of our restructuring in April 2003, we reduced the number of employees in general and administrative positions to levels comparable to the first nine months of 2002.

Compensation expense related to stock options for the three months ended March 31, 2004 was $3.2 million, compared to $9,000 for the same period in 2003, which primarily consisted of compensation expense related to stock options associated with the employee stock option exchange program initiated in April 2003. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with *Accounting Principles Board Opinion No. 25* and *Financial Accounting Standards Board Interpretation No. 44.*

Investment Income

Investment income for the three months ended March 31, 2004 totaled $1.1 million, compared to $1.6 million for the same period in 2003. The $500,000 decrease in investment income for the first three months of 2004 over 2003 is primarily due to our lower average cash balance for the first three months of 2004 compared to the first three months of 2003. In addition, our investment income was affected by the decline in interest rates as a result of current market conditions.

Interest Expense

Interest expense for the three months ended March 31, 2004 totaled $5.1 million, compared to $4.6 million for the same period in 2003. This increase was due to the effect of a higher debt balance due to Lilly as of March 31, 2004, compared to March 31, 2003, and was primarily offset by a decrease in the average interest rate on our debt. We will continue to make quarterly draw-downs on our $100.0 million loan from Lilly of approximately $5.0 million per quarter through March 2005. As a result, we expect our interest expense to increase throughout 2004.

Net Loss Applicable to Common Stock

For the three months ended March 31, 2004 and 2003, we reported a net loss applicable to common stock of $26.5 million and $24.5 million respectively. Our net loss applicable to common stock included $200,000 of accreted dividends on preferred stock for the three months ended March 31, 2004 and 2003. The increase in net loss applicable to common stock was primarily the result of a $3.2 million increase in stock compensation expense, a $1.7 million decrease in revenue, a $500,000 increase in interest expense, and a $500,000 decrease in investment income. The net effect of these changes was offset in part by a decrease of $1.3 million in research and development expenses. In addition, during the three months ended March 31, 2003, we incurred a charge of $2.4 million related to other-than-temporary impairments of our investments in ATL and Hybridon, and there were no such charges incurred during the same period in 2004.

Liquidity and Capital Resources

We have financed our operations with revenue from research and development under collaborative agreements and from affiliates. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through March 31, 2004, we have earned approximately $412.8 million in revenue from contract research and development and from the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $591.3 million from the sale of equity securities. We have borrowed approximately $365.2 million under long-term debt arrangements to finance a portion of our operations.

As of March 31, 2004, we had cash, cash equivalents and short-term investments totaling $180.9 million and working capital of $169.2 million. In comparison, we had cash, cash equivalents and short-term investments of $215.5 million and working capital of $194.0 million as of December 31, 2003. The decreases in our cash, cash equivalents and short-term investments and working capital were due primarily to cash used to fund our operations to purchase property, plant, and equipment, and to pay our debt and capital lease obligations. In addition, we made a $10.0 million cash investment in Alnylam as part of our strategic alliance with them.

As of March 31, 2004, our debt and other obligations totaled $249.5 million, compared to $250.6 million at December 31, 2003. Our debt and other obligations at March 31, 2004 include current and long-term deferred contract revenue of approximately $19.6 million and contractual obligations that represent our payment obligations. The decrease in our debt and other obligations is primarily due to the repayment of convertible partner debt from Boehringer Ingleheim International BmbH, or BI, of approximately $6.4 million. In addition, we repaid principal and interest related to our standard operating debt and certain of our capital leases. The decreases were offset by an additional draw down from the $100.0 million interest-free loan from Lilly, which we discounted to its present value by imputing interest on the amount at 20% and accreting to its face value over its term by recording interest

expense. We also financed $1.3 million in capital additions under our existing capital lease financing arrangement. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required to support our business. We will continue to use lease financing as long as the terms remain commercially attractive. Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe that our available cash, cash equivalents and short-term investments as of March 31, 2004, when combined with investment income and committed contractual cash payments from our partners, will be sufficient to meet our anticipated requirements through at least the end of 2006. The following table summarizes our contractual obligations as of March 31, 2004. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided in the paragraphs following the table:

	Payments Due by Period (in thousands)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
Lilly Research Collaboration Loan	$ 80.0	$ —	$ 80.0	$ —	$ —
5 1/2% Convertible Subordinated Notes	$ 125.0	$ —	$ —	$ —	$ 125.0
Standard Operating Debt	$ 37.8	$ 6.7	$ 19.0	$ 12.1	$ —
Capital Lease Obligations	$ 6.7	$ 3.7	$ 3.0	$ —	$ —
Operating Leases	$ 11.7	$ 2.7	$ 5.6	$ 2.3	$ 1.1

Our contractual obligations consist primarily of our Lilly research collaboration loan and publicly traded convertible debt that we can repay on favorable terms with equity. In addition, we also have standard operating debt, capital leases and other obligations. Our standard operating debt includes a $30.5 million term loan from Silicon Valley Bank, and our mortgage loan payable to another bank.

In December 2003, we secured a $32.0 million term loan from Silicon Valley Bank to retire our existing debt to BI and Elan. We amortize the term loan over sixty months. The term loan requires equal monthly payments of principal plus accrued interest, and bears interest at the prime interest rate, which was 4% at March 31, 2004. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate, and certain equity investments. The loan is subject to certain liquidity requirements, including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate, plus 1.25%. We used the proceeds from the loan to pay off existing debt to Elan of $5.1 million plus accrued interest and to BI of $22.6 million plus accrued interest, of which $6.4 million plus accrued interest we paid during January 2004. The carrying value of the term loan at March 31, 2004 and December 31, 2003 was $30.5 million and $32.0 million, respectively.

In May 2002, we completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. The subordinated notes bear interest at 5½%, which is payable semi-annually, and mature in May 2009. Holders of the subordinated notes can, at any time, convert the notes into shares of common stock at a conversion price of $16.625 per share. At March 31, 2004 and December 31, 2003, the principal outstanding on the notes was $125.0 million.

In August 2001, Lilly made available to us a $100.0 million interest-free loan to fund the joint research collaboration between the two companies. The loan is interest-free and is repayable, at our option, in cash or common stock at $40 per share at the end of four years. The term of the loan provides for quarterly draw downs by us. As of March 31, 2004, we had drawn down $80.0 million of the $100.0 million available. We are accounting for this loan using an imputed interest rate of 20%, consistent with market conditions in place at the time the loan was agreed to. We carry the net present value of the drawdowns as a long-term obligation and record interest expense over the term of the loan. The difference between the cash received and the present value of the loan represents value given to us by Lilly to help fund the research collaboration, and we are accounting for the difference as deferred revenue related to the collaboration, which is recognized as revenue over the period of performance. As of March 31, 2004, the balance in long-term obligations was $60.4 million and the balance in deferred revenue was $19.6 million.

Prospective Information

We recently announced the extension of our antisense cancer drug discovery collaboration with Lilly. During this extension, Lilly and we will continue to characterize and develop RNase H, siRNA, and splicing modulating inhibitors for the treatment of cancer using second and third generation chemistries. An important component of this extension will be the exploration of potential new anticancer drug targets using RNA-directed technologies. This oncology relationship, initiated in June 2002, builds on a broad, ongoing strategic alliance previously established by our two companies to discover antisense drugs in the areas of inflammatory and metabolic diseases.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this Form 10-Q, you should carefully consider the risks described below before purchasing our securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

If we or our partners fail to obtain regulatory approval for our products, we will not be able to sell them.

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drug candidates before a drug candidate can be approved for sale. We must conduct these trials in compliance with U.S. Food and Drug Administration regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drug candidates, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug candidate. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drug candidates. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug candidate, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute products. If we fail to comply with these regulations, regulators could force us to withdraw a drug candidate from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other drug candidates will be safe and effective, will be approved for commercialization or that our partners or we can successfully commercialize these drug candidates.

If the results of clinical testing indicate that any of our drugs under development, including Affinitak and alicaforsen, are not suitable for commercial use, or if additional testing is required to demonstrate suitability, we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease, the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings, and the risk that a compound is not safe or effective for use in humans. Antisense technology in particular is relatively new and unproven. We are applying most of our resources to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drug candidates, including some that remain in our pipeline, that have not resulted in proof of efficacy against targeted indications.

In March 2003, we reported the results of our Phase III clinical trial of Affinitak in patients with late stage non-small cell lung cancer. In this trial, Affinitak, when added to carboplatin and paclitaxol, failed to demonstrate improved survival sufficient enough to support an NDA filing. A similar result could occur with the Affinitak trial Lilly is currently conducting as well as the trials for our other drugs. In 2004, we expect to report the results of our Phase III

clinical trials of alicaforsen in patients with active Crohn's disease. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

If the market does not accept our products, we are not likely to generate revenues or become profitable.

Our success will depend upon the medical community, patients and third-party payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially available product, Vitravene, a treatment for cytomegalovirus, or CMV, retinitis in AIDS patients, which addresses a small market. Our partners and we may not successfully commercialize additional products.

The degree of market acceptance for any of our products depends upon a number of factors, including:

- The receipt and scope of regulatory approvals;
- The establishment and demonstration in the medical and patient community of the efficacy and safety of our drug candidates and their potential advantages over competing products;
- The cost and effectiveness of our drug candidates compared to other available therapies;
- The patient convenience of the dosing regimen for our drug candidates; and
- Reimbursement policies of government and third party payors.

Based on the profile of our drug candidates, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, or if we cannot obtain additional partners, we may have to delay or stop progress on our drug development programs.

We have entered into collaborative arrangements with third parties to develop certain product candidates. We enter into these collaborations in order to:

- Fund our research and development activities;
- Access manufacturing by third parties;
- Seek and obtain regulatory approvals;
- Conduct clinical trials; and
- Successfully commercialize existing and future product candidates.

If any of our partners fail to develop or sell any drug in which we have retained a financial interest, our business may suffer. These collaborations may not continue or result in commercialized drugs. Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. Examples of terminated collaborations include the termination in 2002 of our HepaSense and Orasense collaborations with Elan and the termination of our collaboration with Merck to develop ISIS 113715.

We are collaborating with Lilly to develop Affinitak, our most advanced drug candidate, with Lilly funding Affinitak's development. Lilly could decide to discontinue its funding of Affinitak at any time. The results of our Phase III clinical trial for Affinitak, the market potential of Affinitak or negative results from Lilly's Phase III clinical trial for Affinitak could influence Lilly's decision to discontinue funding of future Affinitak activities.

Other drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, OncoGenex Technologies Inc. and Lilly. We have received significant financial support from U.S. Government-funded grants and contracts for our Ibis program and the development of our

TIGER biosensor. The U.S. Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations. If any of these pharmaceutical company or government partners stopped funding and/or developing these products, our business could suffer.

Certain of our partners are pursuing other technologies or developing other drug candidates either on their own or in collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. Competition may negatively impact a partner's focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of a drug candidate.

Historically, corporate partnering has played a key role in our strategy to fund our development programs and to add key development resources. We plan to continue to rely on additional collaborative arrangements to develop and commercialize our products. However, we may not be able to negotiate additional attractive collaborative arrangements, and, even if negotiated, the collaborative arrangements may not be successful.

In addition, the disappointing results of our first Affinitak Phase III trial could cause our existing partners to reevaluate their commitment to our drug discovery platforms or could impair our ability to attract new collaborative partners. If any of our collaborative partners withdraw their resources or if we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drug candidates could suffer.

We have incurred losses, and our business will suffer if we fail to achieve profitability in the future.

Because drug discovery and development and research services require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of March 31, 2004, our accumulated losses were approximately $582.1 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

We may not successfully develop or derive revenues from our business based on our TIGER biosensor to identify infectious organisms.

Our TIGER biosensor is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires additional research and development prior to marketing. If our potential customers fail to purchase our biosensor due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we could lose our investment in this technology and our TIGER business could fail to meet our business and financial objectives.

If we fail to obtain timely funding, we may need to curtail or abandon some of our programs.

All of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments as of March 31, 2004, combined with investment income and committed contractual cash payments will be sufficient to meet our anticipated requirements through at least the end of 2006. If we do not meet our goals to commercialize our drug products and research services or to license our proprietary technologies, we may need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- the profile and launch timing of our drugs;
- continued scientific progress in our research, drug discovery and development programs;
- the size of these programs and progress with preclinical and clinical trials;

- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in developing and commercializing a business based on our TIGER biosensor to identify infectious organisms; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available, we may have to cut back on one or more of our research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

If we cannot manufacture our products or contract with a third party to manufacture our products at costs that allow us to charge competitive prices to buyers, we will not be able to market products profitably.

If we successfully commercialize any of our drug candidates, we may be required to establish large-scale commercial manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. We have limited experience manufacturing pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, on a commercial scale for the systemic administration of a drug. There are a small number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

Also, manufacturers, including us, must adhere to the FDA's current Good Manufacturing Practices regulations which the FDA enforces through its facilities inspection program. We and our contract manufacturers may not be able to comply or maintain compliance with Good Manufacturing Practices regulations. Non-compliance could significantly delay our receipt of marketing approval for potential products or result in FDA enforcement action after approval that could limit the commercial success of our potential product.

If the results of our Phase III trials for alicaforsen are positive and we fail to secure a marketing and distribution partner for this product, our commercialization efforts for alicaforsen may be harmed or delayed.

We have limited personnel with experience in marketing, selling and distributing products. We expect to depend on third parties to commercialize alicaforsen if our Phase III trials for alicaforsen are positive and we receive marketing approval. If we are unable to reach agreements with suitable third parties, we may fail to meet our business objectives for alicaforsen. We may not successfully establish a collaboration or be able to make alternative arrangements. Moreover, a collaboration or other arrangement we secure may not succeed.

If we fail to compete effectively, our products will not contribute significant revenues.

Our competitors are engaged in all areas of drug discovery throughout the world, are numerous, and include, among others, major pharmaceutical companies and specialized biopharmaceutical firms. Other companies are engaged in developing antisense technology or unique methods of identifying infectious organisms. Our competitors may succeed in developing drug candidates or technologies that are more effective than any drug candidates or technologies that we are developing. These competitive developments could make our products obsolete or non-competitive.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of

products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

If we cannot protect our patents or our proprietary rights, others may compete more directly against us.

Our success depends to a significant degree upon our ability to continue to develop and secure intellectual property rights to proprietary products and services. However, we may not receive issued patents on any of our pending patent applications in the United States or in other countries. In addition, the scope of any of our issued patents may not be sufficiently broad to provide us with a competitive advantage. Furthermore, our issued patents or patents licensed to us may be successfully challenged, invalidated or circumvented so that our patent rights would not create an effective competitive barrier.

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve litigation or proceedings declared by the U.S. Patent and Trademark Office, the International Trade Commission, or foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to such intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or applications held by others that relate to our business. This is especially true since patent applications in the U.S. are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

If we do not progress in our programs as anticipated, the price of our securities could decrease.

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, like when a certain product candidate will enter the clinic, when we will complete a clinical trial, or when we will file an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If we do not achieve milestones when we expect to, investors could be disappointed and the price of our securities would likely decrease. For example, since the data from our Phase III trial for Affinitak were not sufficiently positive to support a single study NDA, we now must wait for the results of Lilly's ongoing Phase III Affinitak trial before we reevaluate whether the data are sufficiently positive to support filing an NDA for Affinitak. We expect results from this second Phase III trial in the second half of 2004.

If Macugen does not achieve marketing approval or its commercial success does not meet our expectations, we will not receive milestone and royalty payments.

As part of our license agreement with Eyetech, we are entitled to receive milestones and royalty payments. However, if Eyetech does not achieve these milestones or receive marketing approval for Macugen, or if Eyetech receives marketing approval for Macugen but fails to commercialize Macugen as expected, we may not receive these payments, or derive the expected value.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could make it more difficult to run our business and reduce our likelihood of success.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to

attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. Failure to succeed in specific clinical trials, including the results of our first Phase III Affinitak trial, may make it more challenging to recruit and retain qualified scientific personnel.

We depend on third parties in the conduct of our clinical trials for our product candidates and any failure of those parties to fulfill their obligations could adversely affect our development and commercialization plans.

We depend on independent clinical investigators, contract research organizations and other third party service providers in the conduct of our clinical trials for our product candidates and expect to continue to do so in the future. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. For example, the investigators are not our employees. However, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Third parties may not complete activities on schedule, or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations could delay or prevent the development, approval and commercialization of our product candidates.

If the price of our securities continues to be highly volatile, this could make it harder for you to liquidate your investment and could increase your risk of suffering a loss.

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding March 31, 2004, the market price of our common stock has ranged from $3.15 to $9.59 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

Provisions in our certificate of incorporation, other agreements and Delaware law may prevent stockholders from receiving a premium for their shares.

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least 66% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, only our board of directors, chairman of the board or chief executive officer can call special meetings of our stockholders. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our company without action by our stockholders.

If registration rights that we have previously granted are exercised, then the price of our securities may be negatively affected.

We have granted registration rights in connection with the issuance of our securities to Elan International Services, Ltd., Eli Lilly and Company, and Reliance Insurance Company. In the aggregate, these registration rights cover approximately 4,166,667 shares of our common stock which are currently outstanding and additional shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these

holders exercise their registration rights, it will bring additional shares of our common stock into the market, which may have an adverse effect on the price of our securities.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to changes in interest rates primarily from our long-term debt arrangements and, secondarily, investments in certain short-term investments. We invest our excess cash in highly liquid short-term investments that are typically held for the duration of the term of the respective instrument. We do not utilize derivative financial instruments, derivative commodity instruments or other market risk sensitive instruments, positions or transactions to manage exposure to interest rate changes. Accordingly, we believe that, while the securities we hold are subject to changes in the financial standing of the issuer of such securities, we are not subject to any material risks arising from changes in interest rates, foreign currency exchange rates, commodity prices, equity prices or other market changes that affect market risk sensitive instruments.

ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of March 31, 2004. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to March 31, 2004.

An evaluation was also performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of any change in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives.

PART II – OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Not applicable

ITEM 2. CHANGES IN SECURITIES AND USE OF PROCEEDS

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

Exhibit Number	Description of Document
10.1	Subcontract No. 44076514 dated February 26, 2004 between Isis Pharmaceuticals, Inc. and Science Applications International Corporation (with certain confidential information deleted).
10.2	Strategic Collaboration and License Agreement dated March 11, 2004 between Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, Inc. (with certain confidential information deleted). (1)
10.3	Investor Rights Agreement dated March 11, 2004 between Isis Pharmaceuticals, Inc. and Alnylam Pharmaceuticals, Inc. (2)
31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

(1) Filed as Exhibit 10.24 to Alnylam Pharmaceutical Inc.'s Registration Statement on Form S-1, File No. 333-113162, and incorporated herein by reference.

(2) Filed as Exhibit 10.25 to Alnylam Pharmaceutical Inc.'s Registration Statement on Form S-1, File No. 333-113162, and incorporated herein by reference.

b. Reports on Form 8-K

On January 7, 2004, the Registrant filed a report on Form 8-K for the announcement of the results of its 176-patient Phase II clinical trial for ISIS 104838 and the related press release dated January 5, 2004.

On February 10, 2004, the Registrant filed a report on Form 8-K for the announcement of its fourth quarter and year ended December 31, 2003 results and the related press release dated February 10, 2004. We furnished this information under Item 12 of Form 8-K, "Results of Operations and Financial Condition."

On May 6, 2004, the Registrant filed a report on Form 8-K for the announcement of its first quarter results and the related press release dated May 6, 2004. We furnished this information under Item 12 of Form 8-K, "Results of Operations and Financial Condition."

(Registrant)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signatures	Title	Date
/s/ STANLEY T. CROOKE Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	May 7, 2004
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	May 7, 2004

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. §§ 200.80(b)4 AND 240.24B-2

SUBCONTRACT AGREEMENT
Time and Material / Labor Hour

SUBCONTRACTOR: Ibis Therapeutics, A Division Of Isis Pharmaceuticals, Inc.
ADDRESS: 2292 Faraday Avenue
Carlsbad, CA. 92008
Attn: Mr. Steven A. Hofstadler
(V) 760-603-2599 (F) 760-603-4653

SUBCONTRACT #: 4400076541
DPAS RATING:
TYPE: Time and Material/Labor Hour
NOT-TO-EXCEED CEILING PRICE: $7,897,000*
Basic Tasks 1-10 Not-To-Exceed $7,767,000
Option Tasks A-E Not – To-Exceed $11,730,000*

INTRODUCTION

This Subcontract Agreement, effective **28 August 2003** is made between SCIENCE APPLICATIONS INTERNATIONAL CORPORATION (hereinafter known as "Buyer"), a Delaware corporation with principal offices in San Diego, California, and **Isis Pharmaceuticals, Inc.** (hereinafter known as "Seller"), a **corporation**, with principal offices in **Carlsbad, CA.** . The effort to be performed by Seller under this Subcontract will be part of Buyer's Prime Contract #**MDA972-00-C-0053** that has been issued by **Defense Advanced Research Projects Agency (DARPA)**. The work, defined in Attachment I (Statement of Work and Schedule) will be performed on a Time and Material/Labor Hour basis, in accordance with Schedule A (Specific Terms and Conditions), and any referenced document in section 17.0 of this agreement.

SCHEDULE A
SPECIFIC TERMS AND CONDITIONS

1.0 PERIOD OF PERFORMANCE

The period of performance for this Subcontract is **28 August 2003** through **30 September 2005**, unless amended in writing by mutual agreement of the parties. Seller is not obligated to continue work or provide services and Buyer is not obligated to compensate Seller for expenses incurred or commitments made before or after these dates.

1.1 LABOR RATES

The following are the Seller's fixed hourly labor rates effective for the period of performance identified in paragraph 1.0 of this Subcontract: Rates incorporated first of November each year via Change Order.

LABOR FOR GFY 03	BILLING RATE	LABOR CATEGORY	BILLING RATE
Executive	$[***] Per hour	Scientist II	$[***] Per hour
Scientist I	$[***] Per hour	Scientist	$[***] Per hour

LABOR FOR GFY 04	BILLING RATE	LABOR CATEGORY	BILLING RATE
Executive	$[***] Per hour	Scientist II	$[***] Per hour
Scientist I	$[***] Per hour	Scientist	$[***] Per hour

LABOR FOR GFY 05	BILLING RATE	LABOR CATEGORY	BILLING RATE
Executive	$[***] Per hour	Scientist II	$[***] Per hour
Scientist I	$[***] Per hour	Scientist	$[***] Per hour

1.2 FUNDING

This Subcontract may be incrementally or fully funded. The Subcontract Ceiling Price of $**7,897,000** **(*Reflects Option A, "Sample Evaluation Funded at $130,000**) is currently funded in the amount of $[***], which is anticipated to cover expenses through **30 September 2005**. And, unless amended in writing by mutual agreement of the parties, Seller is not obligated to incur expenses or make commitments in excess of the Subcontract funded amount, and Buyer is not obligated to compensate Seller beyond the funded amount of the Subcontract. If at any time the Seller has reason to believe that the hourly rate payments and material costs that will accrue in performing this Subcontract in the next succeeding 30 days, if added to all other payments and cost previously accrued will exceed eighty-five percent (85%) of the of the total funded amount of this Subcontract, the Seller shall immediately notify the Buyer in writing providing supporting rationale for additional funds. It is mutually agreed and understood that the above 85% notification requirement applies to each increment of funds provided to Seller under this Subcontract.

1.2.1 OPTIONAL TASKS

Buyer shall have the unilateral right to exercise the Optional Tasks identified below upon written notification to Seller's Contractual Representative no later than thirty (30) days prior to subcontract expiration at the mutually agreed to prices and rates set forth in Section 1.1 of this Subcontract Agreement. These options shall be dependent on approval and adequate funding by the US Government Customer. In addition, Equal Employment Opportunity pre-award approval by the Department of Labor must be obtained prior to award of any options that result in the ceiling value of this subcontract agreement exceeding $10,000,000.

Task	Task Title	Task Value	Revised Ceiling Value
B-1	[***]	[***]	[***]
B-2	[***]	[***]	[***]

B-3	[***]	[***]	[***]
C-1	[***]	[***]	[***]
C-2	[***]	[***]	[***]
C-3	[***]	[***]	[***]
C-4	[***]	[***]	[***]
C-5	[***]	[***]	[***]
D	[***]	[***]	[***]
E	[***]	[***]	[***]

1.3 INSPECTION

All materials furnished and services performed pursuant hereto shall be subject to inspection and test by Buyer and its agents and by its customers at all times and places, during the period of performance, and in any event before acceptance. In the event that material furnished or services supplied are not performed in accordance with the statement of work requirements, Buyer may require Seller to replace or correct services or materials. The cost of replacement or correction shall be determined under the Payment clause of this subcontract, but the "hourly rate" for labor hours incurred in the replacement or correction shall be reduced to exclude that portion of the rate attributable to profit. If the Seller fails to proceed with reasonable promptness to perform required replacement or

correction, and if the replacement or correction cannot be performed within the Not-To-Exceed ceiling price, the Buyer may terminate the subcontract for default.

1.4 INVOICES

Invoices shall be prepared in duplicate and contain the following information; subcontract number, labor categories, hourly rates, labor hours, extended totals by category, material and other direct costs detail shall be separated from labor costs. Invoices will be mailed to:

Science Applications International Corporation
Attention: John M Sterling
Street Address 10260 Campus Point Drive, Bldg. C
City, State, Zip Code San Diego, CA. 92121

Invoices shall clearly reference a unique invoice number on each invoice, period of incurred costs, and the date of the invoice. Invoices shall include the "Amount Previously Billed," the "Amount of this Invoice," the "Withhold Amount", and the "Total Amount Billed to Date" for each labor category. Seller shall submit invoices for the full amount stating the amount of withhold/retention for each line item billed.

Example:	Line Item 1:	$	10,000
	- Less withhold:	$	1,000
	Total Amount Owed:	$	9,000

Invoices shall be signed and dated by the cognizant Contractual Representative of the Seller, verifying the costs included are correct. The following statement will be executed for all invoices whose billing rates are based on fixed hourly rates tied to labor categories that contain minimum education and experience qualifications for assigned personnel:

"I have reviewed the qualifications of the individuals whose labor costs are being invoiced hereunder and hereby confirm that all individuals meet the minimum labor category education and experience requirements for the specific labor categories for which his or her work is being billed."

1.5 PAYMENT

The Buyer shall pay the Seller upon the submission of invoices approved by the Buyer as follows:

(a) *Hourly rate*. The amounts shall be computed by multiplying the appropriate hourly rates in Section 1.1 by the number of direct labor hours performed. Invoices may be submitted once each month to the Buyer. The Seller shall substantiate invoices by evidence of actual payment and by individual daily job time cards, or other substantiation approved by the Buyer. The Buyer shall pay the invoice within 30 days after approval by Buyer. The Buyer shall withhold 5 percent of the amount due under this paragraph, not to exceed $50,000 until execution and delivery of all closeout documentation, acceptable to the Buyer, in accordance with the requirements of paragraph 13.0 herein. Failure to deliver all closeout documentation, including a final invoice showing cumulative payments made, shall be considered to be a material breach of this subcontract, and may subject the subcontractor to forfeiture of the 5% withhold mentioned herein.

(b) Unless specifically authorized in writing by the Buyer, the Seller is not authorized to perform and the Buyer is not obligated to reimburse the Seller for work performed on an Overtime, Extended Work Week, Shift Premium, or Uncompensated Time basis.

(c) *Materials and other direct costs*. Authorized material and other direct costs, such as travel, will be reimbursed on an actual cost basis in accordance with Generally Accepted Accounting Principles applied on a consistent

basis. Where materials are withdrawn from inventories, cost must be determined in accordance with proper accounting practices consistently followed by Seller. Seller shall support all material cost claims by submitting invoices, storeroom requisitions, expense reports, or other substantiation acceptable to Buyer. Reasonable and allocable materials handling costs may be included in the charge for material at cost to the extent they are clearly excluded from hourly rates. The material handling cost shall be 15 % of direct material and other direct costs.

(d) *Total cost*. To the extent the Ceiling Price of this Subcontract is fully funded, it is estimated that the total cost to the Buyer for the performance of this subcontract shall not exceed the ceiling price. The Seller agrees to use its best efforts to perform the work within the ceiling price. If at any time the Seller has reason to believe that the total price to the Buyer will be substantially greater or less than the ceiling price, the Seller shall immediately notify the Buyer in writing and provide a revised estimate for performing the work.

1.6 AUDIT

At any time before final payment the Buyer may request and perform an audit of the invoices and substantiating material. Each payment previously made shall be subject to reduction to the extent of amounts that are found by the Buyer not to have been properly payable in accordance with the payment terms of this subcontract. Audit will include, but not be limited to, individual daily job time cards, invoices for material, storeroom requisitions, expense reports, and other substantiation supporting invoiced amounts.

1.7 WARRANTY

Seller represents and warrants (1) that the rates charged for the goods and/or services purchased pursuant hereto shall be no higher than Seller's current rates to any other customer for the same quality and quantity of such goods or services; (2) that all goods and services delivered pursuant hereto will be new, unless otherwise specified, and free from defects in material and workmanship; (3) that all goods and services will conform to applicable specifications, drawings, and standards of quality and performance, and that all items will be free from defects in design and suitable for their intended purpose; (4) that the goods covered by this order are fit and safe for consumer use, if so intended. All representations and warranties of Seller together with its service warranties and guarantees, if any, shall run to Buyer and Buyer's customers. The foregoing warranties shall survive any delivery, inspection, acceptance, or payment by Buyer.

2.0 TECHNICAL AND CONTRACTUAL REPRESENTATIVES

The following authorized representatives are hereby designated for this Subcontract:

SELLER:		BUYER:	
TECHNICAL:	Mr. Steven Hofstadler	TECHNICAL:	Mr. David W. Robbins
CONTRACTUAL:	Ms. Manolita Villavert	CONTRACTUAL:	Mr. John M. Sterling

2.1 CONTACTS

Contacts with Buyer that affect the subcontract prices, schedule, statement of work, and subcontract terms and conditions shall be made with the authorized contractual representative. No changes to this Subcontract shall be binding upon Buyer unless incorporated in a written modification to the Subcontract and signed by Buyer's contractual representative.

2.2 CHANGES

Buyer may, by written notice to Seller at any time before completion of this subcontract, make changes within the general scope of this subcontract in any one of the following: (a) drawings, designs, or specifications; (b) quantity;

(c) delivery; (d) method of shipment or routing; and (e) make changes in the amount of Buyer furnished property. If any such change causes a material increase or decrease in any hourly rate or the not-to-exceed ceiling price, or the time required for the performance of any part of the work under this subcontract, the Buyer shall make an equitable adjustment in the hourly rates or delivery schedule, or both, and shall modify the subcontract not-to-exceed ceiling price. As a condition precedent to any equitable adjustment, the Seller must notify Buyer in writing of any request for adjustment within twenty (20) days from the date Seller receives notice from Buyer of a change, or from the date of any act of Buyer, which Seller considers to constitute a change. Failure to agree to any adjustment shall be a dispute under the Disputes clause of this subcontract. However, Seller shall proceed with the work as changed without interruption and without awaiting settlement of any such claim.

3.0 DISCLOSURE

Parties not disclose information concerning work under this Subcontract to any third party, unless such disclosure is necessary for the performance of the subcontract effort. No news releases, public announcement, denial or confirmation of any part of the subject matter of this Subcontract or any phase of any program hereunder shall be made without prior written consent of Parties, which consent will not be unreasonably withheld. The restrictions of this paragraph shall continue in effect upon completion or the parties may mutually agree upon termination of this Subcontract for such period of time as in writing. In the absence of a written established period, no disclosure is authorized. Failure to comply with the provisions of this Clause may be cause for termination of this subcontract. The obligations of Paragraph 3.0 will not apply to information that the receiving party can establish by written records was disclosed by the receiving party pursuant to any judicial, government or stock exchange request, requirement or order, so long as the receiving party provides the disclosing party with sufficient prior written notice in order to allow the disclosing party to contest such request, requirement or order.

4.0 KEY PERSONNEL

(a) For purposes of this clause, Buyer and Seller define "Key Personnel" as those individuals who are mutually recognized as essential to the successful completion and execution of this Subcontract.

(b) Personnel designated as "Key Personnel" shall be assigned to the extent necessary for the timely completion of the task to which assigned. Any substitution or reassignment involving Seller's "Key Personnel" assigned to this work shall be made only with persons of equal abilities and qualifications and is subject to prior approval of Buyer, in writing.

(c) Buyer reserves the right to direct the removal of any individual assigned to this Subcontract.

(d) Seller's Key Personnel are: [***]

4.1 IP RIGHTS

Subject to the rights reserved to the U.S. Government under the referenced FAR's, Isis will retain all rights, including commercial rights, to any technology, software and inventions created by Isis during the performance of this Subcontract Agreement ("ISIS Technology"). Inventorship of any invention created hereunder will be determined in accordance with U.S. Patent Law, including joint inventorship, if any, between SAIC and Isis. The ISIS Technology disclosed to SAIC hereunder is disclosed solely for use in performance of SAIC's obligations to the U.S. Government under Prime Contract MDA972-00-C-0053. Any other use of Isis Technology by SAIC, including the pursuit of commercial opportunities, will be subject to separate agreements.

5.0 ASSIGNMENTS AND SUBCONTRACTS

This Subcontract is not assignable and shall not be assigned by Seller without the prior written consent of Buyer. Further, Seller agrees to obtain Buyer's approval before subcontracting this order or any substantial portion thereof; provided, however, that this limitation shall not apply to the purchase of standard commercial supplies or raw materials.

6.0 INSURANCE

Without prejudice to Seller's liability to indemnify Buyer as stated in the INDEMNIFICATION provision of this Agreement, Seller shall procure, at its expense, and maintain for the duration of the Agreement, the insurance policies described below with financially responsible insurance companies, reasonably acceptable to Buyer, with policy limits not less than those indicated below. Notwithstanding any provision contained herein, the Seller, and its employees, agents, representatives, consultants and lower-tier subcontractors and suppliers, are not insured by Buyer, and are not covered under any policy of insurance that Buyer has obtained or has in place.

Special Provisions Applicable to Seller's Insurance coverage:

1. Additional Insured - Seller shall have all policies, except Workers' Compensation and Employer's Liability, endorsed to name Buyer as an Additional Insured with respect to the work to be performed by the Seller.

2. Waiver of Subrogation - Seller shall have all policies endorsed to waive the insurer's rights of subrogation in favor of Buyer except for Workers Compensation.

3. Deductibles - Subject to the reasonable review and approval of Buyer, the Seller may arrange deductibles or self-insured retention's as part of the required insurance coverage's. However, it is expressly agreed that all deductibles or self-insured retention's are the sole responsibility of the Seller.

4. Adequacy of Insurance Limits - The insurance coverage limits stated below are minimum coverage requirements, not limits of liability, and shall not be construed in any way as Buyer's acceptance of responsibility of the Seller.

5. Certificates of Insurance - Prior to commencement of any work under this Agreement, the Seller shall furnish Buyer with Certificates of Insurance covering the current period of performance of this Subcontract, in a format acceptable to Buyer, evidencing the insurance coverage required in this Agreement and containing the following information:

    a. Identify Buyer as an "Additional Insured" with respect to all policies except Workers' Compensation and employers' liability.

    b. State that all policies have been endorsed to waive subrogation in favor of Buyer except for Workers' Compensation.

    c. State that the underwriters agree to provide Buyer with at least 30 days prior written notice of any cancellation in the coverage.

In addition, the Seller shall furnish the Buyer revised Certificates of Insurance covering any and all subsequent extensions to the initial period of performance of this Subcontract.

6.1 COVERAGE

A. Workers' Compensation - Insurance for statutory obligations imposed by law including, where applicable, coverage under United States Longshoremen's and Harbor Workers' Act and Jones Act. (if applicable, Defense Base Act for those employees working on a U.S. Military installation outside of the United States).

B. Employers Liability - Insurance with limits of $1,000,000 for bodily injury by accident and $1,000,000 for bodily injury by disease, including, if applicable, maritime coverage endorsement.

C. Commercial General Liability - (Standard ISO occurrence form) - including full fire legal liability and contractual liability, with a per occurrence limit of $1,000,000.

D. Business Auto Liability - Coverage for bodily injury and property damage liability for all owned, hired or non-owned vehicles, with an each accident limit of $1,000,000.

The following clauses are applicable to this Agreement if checked:

E. Professional Liability - - $1,000,000 per occurrence and aggregate providing coverage for claims arising out of the performance of professional services, resulting from any error, omission or negligent act of the Seller.

7.0 INDEMNIFICATION

(a) Seller shall indemnify, defend and hold SAIC and SAIC's customers harmless from and against any and all damages, losses, liabilities and expenses (including reasonable attorneys' fees) arising out of or relating to any claims, causes of action, lawsuits or other proceedings, regardless of legal theory, that result, in whole or in part, from Seller's (or any of Seller's subcontractors, suppliers, employees, agents or representatives): (i) intentional misconduct, negligence, or fraud, (ii) breach of any representation, warranty or covenant made herein, or (iii) products or services including, without limitation, any claims that such products or services infringe any United States patent, copyright, trademark, trade secret or any other proprietary right of any third party.

(b) Buyer shall promptly notify Seller of any claim against Buyer that is covered by this indemnification provision and shall authorize representatives of Seller to settle or defend any such claim or suit and to represent Buyer in, or to take charge of, any litigation in connection therewith.

8.0 INFRINGEMENT INDEMNITY

(a) In lieu of any warranty by Buyer or Seller against infringement, statutory or otherwise, it is agreed that Seller shall defend, at its expense, any suit against Buyer or its customers based on a claim that any item furnished under this order or the normal use or sale thereof infringes any U.S. Letters patent or copyright, and shall pay costs and damages finally awarded in any such suit, provided that Seller is notified in writing of the suit and given authority, information, and assistance at Seller's expense for the defense of same. If the use or sale of said item is enjoined as a result of such suit, Seller, at no expense to Buyer, shall use commercially reasonable efforts to obtain for Buyer and its customers the right to use and sell said item or shall substitute an equivalent item acceptable to Buyer and extend this patent indemnity thereto.

(b) Notwithstanding the foregoing paragraph, when this order is performed under the Authorization and Consent of the U.S. Government to infringe U.S. Patents, Seller's liability for infringement of such Patents in such performance shall be limited to the extent of the obligation of Buyer to indemnify the U.S. Government.

9.0 CONFIDENTIALITY OF EQUIPMENT AND DATA

Seller agrees that it will keep confidential the features of any equipment, tools, gauges, patterns, designs, drawings, engineering data or other technical or proprietary information furnished by Buyer and use such items only in the performance of this Order or other orders from Buyer and not otherwise, unless Buyer's written consent is first obtained. Seller also agrees to use any designs or data in accordance with any restrictive legends placed on such items by the Buyer or any third party. Upon completion or termination of this Order, Seller shall return all such items to Buyer or make such other disposition thereof as may be directed or approved by Buyer.

10.0 DISPUTES

Any dispute not disposed of in accordance with the "Disputes Clause" of Schedule B, if any, shall be determined in the following manner.

(a) Buyer and Seller agree to enter into Negotiation to resolve any dispute. Both parties agree to negotiate in good faith to reach a mutually agreeable settlement within a reasonable amount of time.

(b) If negotiation is unsuccessful, Buyer and Seller agree to enter into binding Arbitration. The American Arbitration Association (AAA) Commercial Arbitration Rules (most recent edition) are to govern this Arbitration.

The Arbitration shall take place in the County of San Diego, State of California. The Arbitrator shall be bound to follow the applicable subcontract provisions and California law in adjudicating the dispute. It is agreed by both parties that the Arbitrator's decision is final, and that no party may take any action, judicial or administrative, to overturn this decision. The judgment rendered by the Arbitrator may be entered in any court having jurisdiction thereof.

Pending any decision, appeal or judgment referred to in this provision or the settlement of any dispute arising under this Subcontract, Seller shall proceed diligently with the performance of this Subcontract.

11.0 DEFAULT

(a) The Buyer may, by written notice of default to the Seller, terminate the whole or any part of this Subcontract in any one of the following circumstances: (i) if Seller fails to make progress in the work so as to endanger performance delivery of the supplies or to perform the services within the time specified herein or any extension thereof; or (ii) if Seller fails to perform any of the other provisions of this Subcontract in accordance with its terms, and in either of these two circumstances does not cure such failure within a period of 10 days (or such longer period as Buyer may authorize in writing) after receipt of notice from the Buyer specifying such failure; or (iii) Seller becomes insolvent or the subject of proceedings under any law relating to bankruptcy or the relief of debtors or admits in writing its inability to pay its debts as they become due.

(b) If this Subcontract is so terminated, Seller shall submit a final termination settlement proposal to the Buyer. The Seller shall submit the proposal promptly but no later than six (6) months from the effective date of the termination. If Seller fails to submit the proposal within the time allowed, the Buyer may determine the amount, if any, due the Seller because of the termination. The amount will be determined as follows; (i) An amount for direct labor hours determined by multiplying the number of direct labor hours expended before the effective date of termination by the hourly rates, less profit, in the Schedule, less any hourly rate payments already made to the Seller; (ii) An amount for material expenses incurred before the effective date of termination, not previously paid to the Seller. Buyer may procure or otherwise obtain, upon such terms and in such manner as Buyer may deem appropriate, supplies or services similar to those terminated, Seller, subject to the exceptions set forth below, shall be liable to Buyer for any excess costs of such similar supplies or services.

(c) Seller shall transfer title and deliver to Buyer, in the manner and to the extent requested in writing by Buyer at or after termination such complete articles, partially completed articles and materials, parts, tools, dies, patterns, jigs, fixtures, plans, drawings, information and contract rights as Seller has produced or acquired for the performance of the terminated part of this Subcontract, and Buyer will pay Seller the contract price for complete articles delivered to and accepted by Buyer and the fair value of the other property of Seller so requested and delivered.

(d) Seller shall continue performance of this Subcontract to the extent not terminated. Buyer shall have no obligations to Seller with respect to the terminated part of this Subcontract except as herein provided. In case of Seller's default, Buyer's rights as set forth herein shall be in addition to Buyer's other rights although not set forth in this Subcontract.

(e) Seller shall not be liable for damages resulting from default due to causes beyond the Seller's control and without Seller's fault or negligence, provided, however, that if Seller's default is caused by the default of a subcontractor or supplier, such default must arise out of causes beyond the control of both Seller and subcontractor or supplier, and without the fault or negligence of either of them and, provided further, the supplies or services to be furnished by the subcontractor or supplier were not obtainable from other sources.

12.0 SUBCONTRACT CLOSEOUT

Within sixty-calendar days after the end of the period of performance for the services to be procured herein, as described in the Attachment I Statement of Work and the satisfactory performance of which shall be solely determined by Buyer, Buyer will issue to Seller a Subcontract Closeout Package. The Package will include, as

applicable, Subcontractor Release of Claims; Subcontractor's Assignment of Refunds, Rebates, Credits, and Other Amounts; Subcontract Patents Report; and any other documentation or request for information considered necessary by Buyer to closeout this Subcontract Agreement.

Seller agrees to submit all information and documentation, including a FINAL invoice bearing the statement, "*This FINAL invoice was prepared using final audited rates*" as required by the Subcontract Closeout Package within thirty-calendar days of the date of the Package. The parties further agree if the information and documentation submitted by Buyer, finds Seller acceptable with or without negotiations (the necessity for which shall be solely determined by Buyer), to be bound by Seller's closeout submission as the final agreement between the parties with respect thereto.

In the event Seller fails to submit the required closeout information and documentation in a timely manner, such failure shall constitute Seller's express agreement that the amounts paid to date by Buyer pursuant to this Agreement, as determined by Buyer's records, constitute the full, complete and final extent of Buyer's financial obligation to Seller, that Seller does forever fully and finally remise, release, and discharge Buyer, its officers, agents and employees, of and from any and all liabilities, obligations, claims, and demands whatsoever arising under or relating to this Subcontract Agreement, and that Seller expressly authorizes Buyer to rely on the foregoing representations and release in connection with Buyer's closeout of or other actions taken with respect to Buyer's contract with the Government. Furthermore, such failure is considered to be a material breach of the terms of this subcontract, and may subject seller to forfeiture of all or part of the fee withhold prescribed by Article 1.4.

13.0 GENERAL RELATIONSHIP

The Subcontractor is not an employee of SAIC for any purpose whatsoever. Seller agrees that in all matters relating to this Subcontract it shall be acting as an independent contractor and shall assume and pay all liabilities and perform all obligations imposed with respect to the performance of this Subcontract. Seller shall have no right, power or authority to create any obligation, expressed or implied, on behalf of Buyer and/or the Government and shall have no authority to represent Buyer as an agent.

14.0 NON-WAIVER OF RIGHTS

The failure of Buyer to insist upon strict performance of any of the terms and conditions in the Subcontract, or to exercise any rights or remedies, shall not be construed as a waiver of its rights to assert any of the same or to rely on any such terms or conditions at any time thereafter. The invalidity in whole or in part of any term or condition of this subcontract shall not affect the validity of other parts hereof.

15.0 APPLICABLE STATE LAW AND COMPLIANCE

This Subcontract shall be governed by and construed in accordance with the laws of the State of California. Seller agrees to comply with the applicable provisions of any federal, state or local law or ordinance and all orders, rules and regulations issued there under.

16.0 EXPORT CONTROL COMPLIANCE FOR FOREIGN PERSONS

The subject technology of this Subcontract (together including data, services, and hardware provided hereunder) may be controlled for export purposes under the International Traffic in Arms Regulations (ITAR) controlled by the U.S. Department of State or the Export Administration Regulations ("EAR") controlled by the U.S. Department of Commerce. ITAR controlled technology may not be exported without prior written authorization and certain EAR technology requires a prior license depending upon its categorization, destination, end-user and end-use. Exports or re-exports of any U.S. technology to [any destination under U.S. sanction or embargo are forbidden.

Access to certain technology ("Controlled Technology") by Foreign Persons (working legally in the U.S.), as defined below, may require an export license if the Controlled Technology would require a license prior to delivery to the Foreign Person's country of origin. SELLER is bound by U.S. export statutes and regulations and shall comply with all U.S. export laws. SELLER shall have full responsibility for obtaining any export licenses or authorization required to fulfill its obligations under this Subcontract.

SELLER hereby certifies that all SELLER employees who have access to the Controlled Technology are U.S. citizens, have permanent U.S. residency or have been granted political asylum or refugee status in accordance with 8 U.S.C. 1324b(a)(3). Any non-citizens who do not meet one of these criteria are "Foreign Persons" within the meaning of this clause but have been authorized under export licenses to perform their work hereunder.

17.0 ORDER OF PRECEDENCE

The documents listed below are hereby incorporated by reference. In the event of an inconsistency or conflict between or among the provisions of this Subcontract, the inconsistency shall be resolved by giving precedence in the following order:

1. Attachment I: Statement of Work and Schedule dated 07/16/03 (9 Pages).
2. Schedule A: Specific Terms and Conditions Form 9-932-025 (Rev.09/19/03).
3. Schedule B Part I: U.S. Government Terms and Conditions Form 9-932-031 (Rev. 7/00).
4. Schedule B Part II: Contract Clauses (specific for the U.S. Government Agency) (Rev.11/00)
5. U.S. Government Property Enclosure 6, "Without an Approved Gov't Property System". (08/01)

18.0 ENTIRE AGREEMENT

The parties hereby agree that this Subcontract, including all documents incorporated herein by reference, shall constitute the entire agreement and understanding between the parties hereto and shall supersede and replace any and all prior or contemporaneous representations, agreements or understandings of any kind, whether written or oral, relating to the subject matter hereof.

In witness whereof, the duly authorized representatives of Buyer and the Seller have executed this Subcontract on the dates shown.

SELLER:

	SCIENCE APPLICATIONS INTERNATIONAL CORPORATION
Isis Pharmaceuticals, Inc. (Company Name)	
X /s/ B. Lynne Psrshall (Signature)	X /s/ John Sterling (Signature)
NAME: (Type or Print)	**NAME:** (Type or Print)
TITLE:	**TITLE:**
DATE:	**DATE:**

Attachment I
Statement of Work

[***]

SCHEDULE B
U.S. GOVERNMENT TERMS AND CONDITIONS
Applicable to all U.S. Government subcontracts
MDA972-00-C-0053 – T&M SubK
PART I - FAR CLAUSES

1. DEFINITIONS

In all such clauses, unless the context of the clause requires otherwise, the term "Contractor" shall mean Seller, the term "Contract" shall mean this Order, and the terms "Government," "Contracting Officer" and equivalent phrases shall mean Buyer and Buyer's Purchasing Representative(except with respect to FAR 52.227.12, in which the term "Government" will retain its meaning as seth forth in the FAR), respectively. It is intended that the referenced clauses shall apply to Seller in such manner as is necessary to reflect the position of Seller as a subcontractor to Buyer, to insure Seller's obligations to Buyer and to the United States Government, and to enable Buyer to meet its obligations under its Prime Contract or Subcontract.
The following definitions apply unless otherwise specifically stated:

"Buyer" - the legal entity issuing this Order.
"Purchasing Representative" - Buyer's authorized representative.
"Seller" - the legal entity which contracts with the Buyer.
"This Order" - this contractual instrument, including changes.

“Prime Contract” - the Government contract under which this Order is issued.
“FAR” - the Federal Acquisition Regulation.

2. IDENTIFICATION OF CONTRACT NUMBERS

Government contract numbers shown on this Order shall be included in subcontracts and purchase orders issued by Seller hereunder.

3. DISPUTES

(a) Notwithstanding any provisions herein to the contrary:

(1) If a decision relating to the Prime Contract is made by the Contracting Officer and such decision is also related to this Order, said decision, if binding upon Buyer under the Prime Contract shall in turn be binding upon Buyer and Seller with respect to such matter; provided, however, that if Seller disagrees with any such decision made by the Contracting Officer and Buyer elects not to appeal such decision, Seller shall have the right reserved to Buyer under the Prime Contract with the Government to prosecute a timely appeal in the name of Buyer, as permitted by the contract or by law, Seller to bear its own legal and other costs. If Buyer elects not to appeal any such decision, Buyer agrees to notify Seller in a timely fashion after receipt of such decision and to assist Seller in its prosecution of any such appeal in every reasonable manner. If Buyer elects to appeal any such decision of the Contracting Officer, Buyer agrees to furnish Seller promptly with a copy of such appeal. Any decision upon appeal, if binding upon Buyer, shall in turn be binding upon Seller. Pending the making of any decision, either by the Contracting Officer or on appeal, Seller shall proceed diligently with performance of this Order.

(2) If, as a result of any decision or judgment which is binding upon Seller and Buyer, as provided above, Buyer is unable to obtain payment or reimbursement from the Government under the Prime Contract for, or is required to refund or credit to the Government, any amount with respect to any item or matter for which Buyer has reimbursed or paid Seller, Seller shall, on demand, promptly repay such amount to Buyer. Additionally, pending the final conclusion of any appeal hereunder, Seller shall, on demand, promptly repay any such amount to Buyer. Buyer’s maximum liability for any matter connected with or related to this Order which was properly the subject of a claim against the Government under the Prime Contract shall not exceed the amount of Buyer’s recovery from the Government.

(3) If this Order is issued by Buyer under a Government Subcontract rather than a Prime Contract, and if Buyer has the right under such Subcontract to appeal a decision made by the Contracting Officer under the Prime Contract in the name of the Prime Contractor (or if Buyer is subject to any arbitrator’s decision under the terms of its subcontract), and said decision is also related to this Order, this Disputes Clause shall also apply to Seller in a manner consistent with its intent and similar to its application had this Order been issued by Buyer under a Prime Contract with the Government.

(4) Seller agrees to provide certification that data supporting any claim made by Seller hereunder is made in good faith and that the supporting data is accurate and complete to the best of Seller’s knowledge or belief, all in accordance with the requirements of the Contract Disputes Act of 1978 (41USC601-613) and implementing regulations. If any claim of Seller is determined to be based upon fraud or misrepresentation, Seller agrees to defend, indemnify and hold Buyer harmless for any and all liability, loss, cost or expense resulting therefrom.

(b) Any dispute not addressed in paragraph (a) above, will be subject to the disputes clause of Schedule A of this subcontract agreement.

4. OTHER GOVERNMENT PROCUREMENT

Nothing contained herein shall be construed as precluding the Seller from producing items for direct sale to the Government, utilizing therefore all hardware and/or software, including designs, drawings, engineering data or other technical or proprietary information furnished Seller by Buyer, provided the Government has the unrestricted right to permit the use thereof for such purpose.

5. INDEMNIFICATION - COST OR PRICING DATA - COST ACCOUNTING STANDARDS

Seller agrees to indemnify and hold Buyer harmless to the full extent of any cost or price reduction effected by Buyer’s customer, which may result from (i) certified cost or pricing data submitted by Seller or its lower-tier subcontractors which is not accurate, current or complete as certified by Seller; (ii) the failure by Seller or its lower-tier subcontractors to disclose and consistently follow applicable cost accounting practices and standards or otherwise comply with pertinent parts of the FAR, applicable agency supplements thereto, and regulations promulgated by the Cost Accounting Standards Board.

6. TERMINATION FOR CONVENIENCE

The Buyer may terminate performance of work under this subcontract in whole, or in part if the Purchasing Representative determines that a termination is in the Buyer’s interest. The Buyer shall terminate by delivering to the Seller a Notice of Termination specifying the extent of termination and the effective date. If this is a Fixed Price subcontract, the termination will be in accordance with FAR 52.249-2 and FAR 52.249-4. If this is a Cost Reimbursable subcontract, the termination will be in accordance with FAR 52.249-6. If this is a Cost Reimbursement subcontract for Educational or Other Nonprofit Institutions, then termination will be in accordance with FAR 52.249-5.

7. GOVERNMENT PROPERTY

Seller shall comply with the Government Property requirements contained in FAR clause 52.245-2 if this is a fixed priced contract and FAR clause 52.245-5 (substituting 52.245-2 subparagraph (g) for 52.245-5 subparagraphs (g) (1), (2), and (3) if this is a cost reimbursement contract.

8. CONTRACT COST PRINCIPLES AND PROCEDURES

Seller agrees that to the extent applicable, costs allocated to this contract shall be in full compliance with Subpart 31.2 of FAR (Subpart 31.3 for Educational Institutions) and the applicable agency supplements thereto, if any, set forth in Part II hereof. In the event such compliance is not maintained, Seller agrees to compensate Buyer to the full extent of any prices or costs, including any penalties or interest, which are determined by Buyer’s customer to be unallowable or unreasonable or not allocable, under Buyer’s contract with its customer.

9. FAR CLAUSES APPLICABLE TO THIS ORDER

The clauses in FAR Subpart 52.2 referenced in subparagraph (a), the clauses applicable at the dollar thresholds in subparagraph (b), and those clauses referenced and checked in subparagraph (c) below, in effect on the date of this Order, are incorporated herein and made a part of this Order. To the extent that an earlier version of any such clause is included in the Prime Contract or Subcontract under which this Order is issued, the date of the clause as it appears in such Prime Contract or Subcontract shall be controlling and said version shall be incorporated herein.

(a) The following clauses are applicable to this Order:

Clause No. & FAR Reference	Title of Clause
52.203-3	Gratuities
52.211-5	Material Requirements
52.211-15	Defense Priority and Allocation Requirements
52.222-1	Notice to the Government of Labor Disputes
52.222-26	Equal Opportunity (Only Paragraphs (b)(1) through (b)(11)
52.223-3	Hazardous Material Identification and Material Safety Data
52.225-13	Restrictions on Certain Foreign Purchases
52.229-3	Federal, State, and Local Taxes

(b) The following clauses are applicable to this Order at the indicated dollar values:

Clause No. & FAR Reference	Title of Clause
52.203-5	Covenant Against Contingent Fees (if order exceeds $50,000)
52.203-6	Restrictions on Subcontractor Sales to the Government (if order exceeds $100,000)
52.203-7	Anti-Kickback Procedures (if order exceeds $100,000)
52.203-8	Cancellation, Rescission, and Recovery of Funds for Illegal or Improper Activity
52.203-10	Price or Fee Adjustment for Illegal or Improper Activity (If order exceeds $50,000)
52.203-11	Certification and Disclosure Regarding Payments to Influence Certain Federal Transactions (if order exceeds or is expected to exceed $100,000)
52.203-12	Limitation on Payments to Influence Certain Federal Transactions (if order exceeds or is expected to exceed $100,000)
52.209-6	Protecting the Governments Interest when Subcontracting with Contractors Debarred, Suspended, or Proposed for Debarment (if Order exceeds $25,000)
52.215-2	Audit and Records-Negotiation (if Order exceeds $50,000)
52.219-8	Utilization of Small Business Concerns (if Order exceeds $50,000)
52-219-9	Small Business Subcontracting Plan (if Subcontract exceeds or is expected to exceed $500,000)
52.222-4	Contract Work Hours & Safety Standards Act - Overtime Compensation (if Order exceeds $100,000)
52.222-35	Affirmative Action for Disabled Veterans and Veterans of the Vietnam Era (if Order exceeds $10,000)
52.222-36	Affirmative Action for Workers with Disabilities (if Order exceeds $2,500)
52.222-37	Employment Reports on Special Disabled Veterans and Veterans of the Vietnam Era (if Order exceeds $10,000)
52.227-2	Notice and Assistance Regarding Patent and Copyright Infringement (if Order exceeds $50,000)
52.246-16	Responsibility for Supplies (if order exceeds $50,000)
52.247-63	Preference for U.S. Flag Air Carriers (if order exceeds $50,000)

(c) The following clauses are applicable to this Order if checked:

Clause No. & FAR Reference	Title of Clause
o 52.203-10	Price or Fee Adjustment for Illegal or Improper Activity (If Order exceeds $50,000)
☒ 52.204-2	Security Requirements
o 52.204-4	Printing/Copying Double Sided on Recycled Paper
o 52.207-3	Right of First Refusal of Employment Openings
o 52.214-26	Audit and Records-Sealed Bidding
o 52.214-27	Price Reduction for Defective Cost or Pricing Data Modifications - Sealed Bidding
o 52.214-28	Subcontractor Cost or Pricing Data - Modifications - Sealed Bidding
☒ 52.215-10	Price Reduction for Defective Cost or Pricing Data
o 52.215-11	Price Reduction for Defective Cost or Pricing Data -Modifications
☒ 52.215-12	Subcontractor Cost or Pricing Data
☒ 52.215-13	Subcontractor Cost or Pricing Data - Modifications
☒ 52.215-15	Pension Adjustments and Asset Reversions
o 52.215-16	Facilities Capital Cost of Money
☒ 52.215-18	Reversion or Adjustment of Plans for Post-Retirement Benefits Other Than Pensions
o 52.215-19	Notification of Ownership Changes
o 52.215-20	Requirements for Cost or Pricing Data or Information Other Than Cost or Pricing Data
☒ 52.215-21	Requirements for Cost or Pricing Data or Information Other Than Cost or Pricing Data - Modifications

☒ 52.216-7	Allowable Cost and Payment
o 52.216-8	Fixed Fee
o 52.216-18	Ordering
o 52.216-22	Indefinite Quantity
o 52.217-8	Option to Extend Services
o 52.217-9	Option to Extend the Term of the Contract
	(a) within the current contract year (b) not to exceed 60 months or 5 years
o 52.219-16	Liquidated Damages – Subcontracting Plan
o 52.222-2	Payment for Overtime Premiums -Subparagraph (a) Add “0”
☒ 52.222-3	Convict Labor
o 52.222-6	Davis-Bacon Act (if order is for construction exceeding $2,000)
o 52.222-11	Subcontracts (Labor Standards)
o 52.222-20	Walsh-Healy Public Contracts Act (if Order exceeds $10,000)
☒ 52.222-21	Prohibition of Segregated Facilities
o 52.222-29	Notification of Visa Denial
o 52-222-41	Service Contract Act of 1965, as Amended - (If Order exceeds $2,500)
o 52.222-42	Statement of Equivalent Rates by Federal Hires
o 52.222-43	Fair Labor Standards Act and Service Contract Act - Price Adjustment (Multiple Year and Option Contracts)
o 52.222-46	Evaluation of Compensation for Professional Employees
o 52.223-5	Pollution Prevention and Right-to-Know Information
☒ 52.223-6	Drug-Free Workplace
o 52.223-7	Notice of Radioactive Materials
☒ 52.223-14	Toxic Chemical Release Reporting
o 52.224-2	Privacy Act
o 52.225-1	Buy American Act -Balance of Payments Program - Supplies
o 52.225-5	Trade Agreements
o 52.225-8	Duty-Free Entry
☒ 52.226-1	Utilization of Indian Organizations and Indian -Owned Economic Enterprises
o 52.227-1	Authorization and Consent (if order exceeds $50,000)
☒ 52.227-1	Authorization and Consent -Alternate I
o 52.227-3	Patent Indemnity (if order exceeds $50,000)
o 52.227-9	Refund of Royalties
☒ 52.227-10	Filing of Patent Applications - Classified Subject Matter
o 52.227-11	Patent Rights - Retention by the Contractor (Short Form)

☒ 52.227-12	Patent Rights - Retention by the Contractor (Long Form)
o 52.227-13	Patent Rights - Acquisition by the Government
o 52.227-14	Rights in Data - General (Alternate I, II, III, IV, or V)
o 52.227-16	Additional Data Requirements
o 52.227-17	Rights in Data - Special Works
o 52.227-18	Rights in Data - Existing Works
o 52.227-19	Commercial Computer Software - Restricted Rights
o 52.227-20	Rights in Data SBIR Program
o 52.227-21	Technical Data, Certification, Revision and Withholding of Payment - Major Systems
o 52.227-22	Major System - Minimum Rights
o 52.227-23	Rights to Proposal Data (Technical)
o 52.228-3	Worker’s Compensation Insurance (Defense Base Act)
o 52.228-4	Worker’s Compensation and War-Hazard Insurance Overseas
o 52.228-5	Insurance - Work on a Government Installation
☒ 52.228-7	Insurance - Liability to Third Persons
o 52.229-6	Taxes - Foreign Fixed-Price Contracts
o 52.229-7	Taxes - Fixed-Price Contracts with Foreign Governments
o 52.229-8	Taxes - Foreign Cost-Reimbursement Contracts
o 52.229-9	Taxes - Cost-Reimbursement Contracts with Foreign Governments
o 52.229-10	State of New Mexico Gross Receipts and Compensating Tax
o 52.230-2	Cost Accounting Standards
o 52.230-3	Disclosure and Consistency of Cost Accounting Practices
o 52.230-5	Cost Accounting Standards -Educational Institution
o 52.230-6	Administration of Cost Accounting Standards
o 52.232-7	Payments Under Time-and-Materials and Labor-Hour Contracts
o 52.232-16	Progress Payments (Notwithstanding paragraph 8 above, in paragraph (d),”Government” means the “U.S. Government” except in subdivision (d)(2)(iv).
o 52.232-17	Interest
o 52.232-18	Availability of Funds
o 52.232-19	Availability of Funds for the Next Fiscal Year
o 52.232-20	Limitation of Cost
☒ 52.232-22	Limitation of Funds
o 52.232-23	Assignment of Claims
o 52.232-23	Assignment of Claims Alternate 1
o 52.232-32	Performance-Based Payments
o 52.236-2	Differing Site Conditions
o 52.236-13	Accident Prevention

o 52.237-2	Protection of Government Buildings, Equipment & Vegetation
o 52.237-3	Continuity of Services
o 52.237-7	Indemnification and Medical Liability Insurance
o 52.237-10	Identification of Uncompensated Overtime
o 52.239-1	Privacy or Security Safeguards
☒ 52.242-1	Notice of Intent to Disallow Costs
☒ 52.242-3	Penalties for Unallowable Costs
☒ 52.242-4	Certification of Final Indirect Costs
o 52.242-12	Report of Shipment
☒ 52.242-13	Bankruptcy
o 52.242-15	Stop-Work Order
☒ 52.242-15	Stop-Work Order Alternate 1
o 52.243-1	Changes - Fixed-Price
o 52.243-1	Changes - Fixed- Price - Alternate I
o 52.243-2	Changes - Cost-Reimbursement
o 52.243-2	Changes - Cost-Reimbursement - Alternate I
o 52.243-2	Changes - Cost-Reimbursement - Alternate II
o 52.243-2	Changes - Cost-Reimbursement - Alternate V
☒ 52.243-3	Changes - Changes - Time-and-Materials or Labor-Hours
o 52.243-6	Change Order Accounting
☒ 52.244-2	Subcontracts (AUG 1998) Alternate I (AUG 1998)

☒ 52.244-5	Competition in Subcontracting
o 52.244-6	Subcontracts for Commercial Items and Commercial Components
o 52.245-4	Government-Furnished Property (Short Form)
☒ 52.245-5	Government Property (Cost-Reimbursement, Time and Material or Labor-Hour Contracts) (JAN 1986) (DEVIATION)
o 52.245-8	Liability for the Facilities
o 52.245-16	Facilities Equipment Modernization
o 52.245-17	Special Tooling
o 52.245-18	Special Test Equipment
☒ 52.245-19	Government Property Furnished “As Is”
o 52.246-1	Contractor Inspection Requirements
o 52.246-2	Inspection of Supplies - Fixed Price
o 52.246-3	Inspection of Supplies - Cost-Reimbursement
o 52.246-4	Inspection of Services - Fixed-Price
o 52.246-5	Inspection of Services - Cost-Reimbursement
o 52.246-6	Inspection of Time-and- Material and Labor-Hour
☒ 52.246-8	Inspection of Research and Development - Cost-Reimbursement
o 52.246-9	Inspection of Research and Development – Short Form (APR 1984)
o 52.246-20	Warranty of Services
o 52.246-23	Limitation of Liability
o 52.246-24	Limitation of Liability - High-Value Items
o 52.246-25	Limitation of Liability – Services
☒ 52.247-1	Commercial Bill of Lading Notation
o 52.247-55	F.o.b. Point for Delivery of Government-Furnished Property
☒ 52.247-64	Preference for Privately Owned U.S. Flag Commercial Vessels
☒ 52.247-67	Submission of Commercial Transportation Bills to the General Services Administration for Audit (JUN 1997)
o 52.248-1	Value Engineering
☒ 52.249-6	Termination (Cost-Reimbursement) (SEP 1996)
o 52.249-8	Default -(Fixed-Price Supply and Services)
o 52.249-14	Excusable Delays
☒ 52.251-01	Government Supply Sources (APR 1984)
o 52.253-1	Computer Generated Forms

SCHEDULE B
CONTRACT CLAUSES

Department of Defense
PART II DFAR CLAUSES
MDA972-00-C-0053 – T&M

1. REFERENCES TO DFAR SUPPLEMENT

All references herein to “DFAR Supplement” or “DFAR SUPP” shall mean the Department of Defense Supplement to the Federal Acquisition Regulation.

2. DFAR SUPPLEMENT CLAUSES APPLICABLE TO THIS ORDER

The clauses in DFAR Supplement Subpart 252.2 referenced in subparagraph (a) and those clauses referenced and checked in subparagraph (b), below, in effect on the date of this Order, are incorporated herein and made a part of this Order. To the extent that an earlier version of any such clause is included in the Prime Contract or Subcontract under which this Order is issued, the date of the clause is it appears in such Prime Contract or Subcontract shall be controlling and said version shall be incorporated therein. In all such clauses, unless the context of a clause requires otherwise, the term "Contractor" shall mean Seller, the term "Contract" shall mean this Order, and the terms "Government," "Contracting Officer" and equivalent phrases shall mean Buyer and Buyer's Purchasing Representative (except with respect to DFARs 252.227-7013, 252.227-7014, and 252.227-7016, in which the term "Government" will retain its meaning as set forth in the DFAR), respectively. It is intended that the referenced clause shall apply to Seller in such manner as is necessary to reflect the position of Seller as a subcontractor to Buyer, to insure Seller's obligations to Buyer and to the United States Government, and to enable Buyer to meet its obligations under its Prime Contract or Subcontract.

(a) The following clauses are applicable to this Order:

DFAR Reference	Title of Clause
252.203-7001	Prohibition on Persons Convicted of Fraud or Other Defense-Contract-Related Felonies)
252.204-7000	Disclosure of Information
252.208-7000	Intent to Furnish Precious Metals as Government-Furnished Material
252.209-7000	Acquisitions From Subcontractors Subject to On-Site Inspection under the Intermediate-Range Nuclear Forces (INF) Treaty (If Subcontract exceeds $25,000)
252.211-7000	Acquisition Streamlining (If Subcontract exceeds $1,000,000)
252.215-7000	Pricing Adjustments
252.217-7003	Changes
252.219-7003	Small, Small Disadvantaged and Women-Owned Small Business Subcontracting Plan (DOD Contracts) (If Order exceeds $500,000)
252.225-7026	Reporting of Contract Performance Outside the United States
252.227-7018	Rights in Noncommercial Technical Data and Computer Software -Small Business Innovation Research (SBIR) Program
252.227-7033	Rights in Shop Drawings
252.227-7034	Patents – Subcontracts
252.227-7037	Validation of Restrictive Markings on Technical Data
252.228-7005	Accident Reporting & Investigation Involving Aircraft, Missiles, and Space Launch Vehicles
252.231-7000	Supplemental Cost Principles
252.247-7001	Price Adjustment

b) DFAR Supplement clauses applicable to this Order if checked:

DFAR Reference	Title of Clause
☒ 252.201-7000	Contracting Officer's Representative (DEC 1991)
☒ 252.204-7003	Control of Government Personnel Work Product
☒ 252.204-7005	Oral Attestation of Security Responsibilities (AUG 1999)
☒ 252.215-7002	Cost Estimating System Requirements (OCT 1998)
☒ 252.223-7004	Drug-Free Work Force
☒ 252.225-7012	Preference for Certain Domestic Commodities
☒ 252.227-7013	Rights in Technical Data Noncommercial Items
☒ 252.227-7014	Rights in Noncommercial Computer Software and Noncommercial Computer Software Documentation
☒ 252.227-7016	Rights in Bid or Proposal Information
☒ 252.227-7017	Identification and Assertion of Use, Release, or Disclosure Restrictions
☒ 252.227-7019	Validation of Asserted Restriction – Computer Software (JUN 1995)
☒ 252.227-7027	Deferred Ordering of Technical Data or Computer Software
☒ 252.227-7030	Technical Data - Withholding of Payment
☒ 252.227-7036	Certification of Technical Data Conformity
☒ 252.235-7010	Acknowledgment of Support and Disclaimer
☒ 252.235-7011	Final Scientific of Technical Report (MAY 1995)
☒ 252.243-7002	Requests for Equitable Adjustments (MAR 1998)
☒ 252.245-7001	Reports of Government Property
☒ 252.247-7023	Transportation of Supplies by Sea (MAR 2000)
☒ 252.247-7024	Notification of Transportation of Supplies by Sea
☒ 252.251-7000	Ordering from Government Supply Sources (MAY 1995)

Exhibit 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 7, 2004

/s/ Stanley T. Crooke

Stanley T. Crooke, M.D., Ph.D.
Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Isis Pharmaceuticals, Inc.;

2. Based on my knowledge, this quarterly report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this quarterly report;

3. Based on my knowledge, the financial statements, and other financial information included in this quarterly report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this quarterly report;

4. The registrant's other certifying officers and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Dated: May 7, 2004

/s/ B. Lynne Parshall

B. Lynne Parshall, J.D.
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc., (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended March 31, 2004, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: May 7, 2004

/s/ Stanley T. Crooke	/s/ B. Lynne Parshall
Stanley T. Crooke, M.D., Ph.D.	B. Lynne Parshall, J.D.
Chief Executive Officer	Chief Financial Officer

A signed original of this written statement required by Section 906 has been provided to Isis Pharmaceuticals, Inc. and will be retained by Isis Pharmaceuticals, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.