UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-Q

(Mark One)

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

For the Quarterly Period Ended September 30, 2004

OR

o 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 November 3, 2004 was 57,277,367.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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

	September 30, 2004 (Unaudited)	December 31, 2003 (Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 21,446	$ 33,117
Short-term investments	104,119	182,387
Contracts receivable	5,464	2,657
Inventory	20,090	13,995
Other current assets	8,236	7,405
Total current assets	159,355	239,561
Property, plant and equipment, net	30,857	34,790
Licenses, net	26,619	28,363
Patents, net	25,981	22,374
Deposits and other assets	8,052	8,479
Long-term investments	4,407	1,375
Total assets	$ 255,271	$ 334,942
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,818	$ 3,720
Accrued compensation	3,819	4,149
Accrued liabilities	10,430	6,527
Current portion of long-term obligations	10,029	16,477
Current portion of deferred contract revenue	15,801	14,684
Total current liabilities	42,897	45,557
5 ½% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	104,369	88,397
Long-term deferred contract revenue, less current portion	644	8,810

Stockholders' equity (deficit):		
Series B Convertible Exchangeable 5% Preferred stock, $0.001 par value; 4,605 shares authorized, no shares issued or outstanding at September 30, 2004; 16,620 shares authorized, 12,015 shares issued and outstanding at December 31, 2003	—	12,015
Accretion of Series B Preferred stock dividends	—	2,560
Common stock, $0.001 par value; 100,000,000 shares authorized, 57,277,367 shares and 55,557,253 shares issued and outstanding at September 30, 2004 and December 31, 2003, respectively	57	56
Additional paid-in capital	622,395	604,948
Deferred compensation	(140)	(294)
Accumulated other comprehensive income	956	3,476
Accumulated deficit	(640,907)	(555,583)
Total stockholders' equity (deficit)	(17,639)	67,178
Total liabilities and stockholders' equity (deficit)	$ 255,271	$ 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 September 30,		Nine Months Ended September 30,	
	2004	2003	2004	2003
Revenue:				
Research and development revenue under collaborative agreements	$ 9,055	$ 11,263	$ 24,270	$ 39,944
Licensing and royalty revenue	38	31	6,969	347
Total revenue	9,093	11,294	31,239	40,291
Operating expenses:				
Research and development	29,566	27,410	90,549	87,849
General and administrative	2,373	2,147	7,394	7,201
Compensation expense (benefit) related to stock options	(466)	804	(649)	936
Restructuring activities	—	—	—	1,803
Total operating expenses	31,473	30,361	97,294	97,789
Loss from operations	(22,380)	(19,067)	(66,055)	(57,498)
Other income (expenses):				
Investment income	561	1,177	2,536	3,980
Interest expense	(5,832)	(4,313)	(16,387)	(13,665)
Loss on investments	(5,057)	—	(5,057)	(2,438)
Net loss	(32,708)	(22,203)	(84,963)	(69,621)
Accretion of dividends on preferred stock	—	(175)	(361)	(518)
Net loss applicable to common stock	$ (32,708)	$ (22,378)	$ (85,324)	$ (70,139)
Basic and diluted net loss per share	$ (0.57)	$ (0.40)	$ (1.51)	$ (1.27)
Shares used in computing basic and diluted net loss per share	57,267	55,540	56,415	55,418

See accompanying notes

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

	Nine Months Ended September 30,	
	2004	2003
Net cash used in operating activities	$ (76,974)	$ (63,065)

Investing activities:		
Purchase of short-term investments	(65,989)	(137,593)
Proceeds from the sale of short-term investments	142,668	144,499
Purchase of property, plant and equipment	(2,413)	(6,138)
Other assets	(5,174)	(4,396)
Strategic investments	(10,000)	—
Investments in affiliates	—	(5,193)
Net cash provided by (used in) investing activities	59,092	(8,821)
Financing activities:		
Net proceeds from issuance of equity	3,316	1,680
Proceeds from long-term borrowings	16,742	28,366
Principal payments on debt and capital lease obligations	(13,847)	(4,224)
Net cash provided by financing activities	6,211	25,822
Net decrease in cash and cash equivalents	(11,671)	(46,064)
Cash and cash equivalents at beginning of period	33,117	101,856
Cash and cash equivalents at end of period	$ 21,446	$ 55,792
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,858	$ 5,168
Supplemental disclosures of non-cash investing and financing activities:		
Conversion of preferred stock into common stock	$ 14,935	$ —
Decrease in property, plant and equipment and notes payable	$ —	$ 21,200
Additions to long-term investments for acquired corporate securities	$ —	$ 750
Decrease in inventory and deferred revenue	$ —	$ 8,750

See accompanying notes

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
September 30, 2004
(Unaudited)

1. Basis of Presentation

The unaudited interim consolidated financial statements for the three and nine-month periods ended September 30, 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, 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 subsidiaries, Isis Pharmaceuticals Singapore Pte Ltd., Hepasense, Ltd., and Orasense, Ltd.

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 ("EITF") Issue No. 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 ("SAB") No. 104, which was issued in December 2003. SAB No. 104 updates portions of the interpretive guidance included in Topic 13 of the codification of SAB No. 101 in order to make this interpretive guidance consistent with current authoritative accounting and auditing guidance and SEC rules and regulations. SAB No. 104 provides interpretation on selected revenue recognition

issues. Under SAB No. 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.

In August 2001, as part of Isis' alliance with Eli Lilly and Company ("Lilly"), Lilly provided Isis a $100.0 million interest free loan to fund the research collaboration. As of September 30, 2004, Isis had drawn down $90.0 million on the $100.0 million loan. Isis discounted the $90.0 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 Statement of Financial Accounting Standards ("SFAS") No. 115, *Accounting for Certain Investments in Debt and Equity Securities*, and carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Isis determines fair value based upon market prices quoted on the last day of the fiscal quarter, and 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"). During the third quarter of 2004, Isis recorded a non-cash loss on investments of $5.1 million principally related to the impairment of the Company's equity investment in Alnylam Pharmaceuticals, Inc. The impairment reflects the decrease in the market value of Alnylam Pharmaceuticals, Inc.'s stock, which Isis believes is primarily a result of current financial market conditions related to biotechnology companies.

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. For example, 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 September 30, 2004 and December 31, 2003 (net realizable value in thousands):

	September 30, 2004	December 31, 2003
Raw materials	$ 3,077	$ 1,526
Work in process	13,079	9,920
Finished goods	3,934	2,549
	$ 20,090	$ 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 Isis' and its partners' clinical trials.

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 No. 144, *Accounting for the Impairment of Long-Lived Assets*, Isis evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, on at least a quarterly basis, and 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 condensed consolidated financial statements and accompanying notes. Actual results could differ from those estimates.

Long-Term Debt

Isis has a $100.0 million Lilly research collaboration loan, of which $90.0 million was outstanding as of September 30, 2004, that comes due in August 2005. Isis can repay this loan at its option in either cash or its common stock at a fixed conversion price of $40 per share. Accordingly, the outstanding balance on this loan has been classified as a long-term obligation in the current quarter.

Consolidation of Variable Interest Entities

Isis has implemented the provisions of Financial Accounting Standards Board Interpretation ("FIN") No. 46, *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51*, which addresses consolidation by business enterprises of variable interest entities 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. As of September 30, 2004, Isis had a collaborative arrangement with Ercole Biotech, Inc. ("Ercole"), a development stage biopharmaceutical company developing drugs based on RNA splicing technology. Isis considers Ercole to be a Variable Interest Entity ("VIE") under the provisions of FIN No. 46. Pursuant to the terms of a Note and Warrant Purchase Agreement (the "Agreement"), during 2003 and early 2004, Isis made cash payments to Ercole of $500,000 and $250,000 respectively; in exchange for a convertible promissory note (the "Note"). Isis expensed the payments when made. The Note is secured by all of Ercole's assets, including intellectual property and licenses, and will convert into securities that Ercole issues in a qualified financing, as defined by the Agreement. Isis is not required to consolidate Ercole's results of operations under FIN No. 46.

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 Accounting Principles Board ("APB") Opinion No. 25 and FIN No. 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 benefit of approximately $466,000 and $649,000 during the three and nine months ended September 30, 2004, respectively.

Isis has adopted the disclosure-only provision of SFAS No. 123, *Accounting for Stock-Based Compensation* ("SFAS 123"). Accordingly, Isis has not recognized compensation expense for the Isis stock option plans, except for compensation expense primarily related to the affected options from the 2000 and 2003 option exchange programs. Had Isis determined compensation expense consistent with SFAS No. 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 September 30,		Nine Months Ended September 30,	
	2004	2003	2004	2003
Net loss applicable to common stock—as reported	$ (32,708)	$ (22,378)	$ (85,324)	$ (70,139)
Net loss applicable to common stock—pro forma	$ (34,775)	$ (23,978)	$ (91,289)	$ (72,728)
Basic and diluted net loss per share—as reported	$ (0.57)	$ (0.40)	$ (1.51)	$ (1.27)
Basic and diluted net loss per share—pro forma	$ (0.61)	$ (0.43)	$ (1.62)	$ (1.31)

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:

	September 30,	
	2004	2003
Risk-free interest rate	4.1%	3.9%

Dividend yield	0%	0%
Volatility	65.3%	76.0%
Expected Life	6.3 years	5.8 years

The weighted average fair values of options granted were $5.40 and $6.70 for the three and nine months ended September 30, 2004, respectively. The weighted average fair values of options granted were $5.36 and $5.74 for the three and nine months ended September 30, 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 September 30,		Nine Months Ended September 30,	
	2004	2003	2004	2003
Comprehensive loss:				
Change in unrealized gains (losses)	$ 3,182	$ 1,358	$ (2,520)	$ 5,042
Net loss applicable to common stock	(32,708)	(22,378)	(85,324)	(70,139)
Comprehensive loss	$ (29,526)	$ (21,020)	$ (87,844)	$ (65,097)

Impact of recently issued accounting standards

In October 2004, the FASB issued Statement 123R, *Share-Based Payment*. The statement is effective at the beginning of the first interim period beginning after June 15, 2005. This statement requires the measurement of compensation costs for all share-based payments to employees, including grants of employee stock options, at fair value. This statement would also eliminate the ability to account for share-based compensation transactions using APB Opinion No. 25. Isis is currently evaluating the effect that the adoption of Statement 123R will have on its financial position and results of operations.

In March 2004, the Financial Accounting Standards Board ("FASB") issued EITF 03-1, *The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments.* EITF 03-1 requires a three-step model to determine other-than-temporary impairments for all current and future investments in marketable securities, which was originally effective for interim and annual reporting periods beginning after June 15, 2004. In September 2004, the FASB delayed the requirement to record impairment losses under EITF 03-1 until new guidance is issued. Isis does not expect that the adoption of EITF 03-1 will have a material impact on its operating results and financial position.

3. Stockholders' Equity

Elan Corporation, plc

In June 2004, Isis entered into an agreement with a subsidiary of Elan Corporation, plc, ("Elan") to acquire Elan's minority interest in Orasense™ and HepaSense™. Through this agreement, Isis eliminated all future royalties to Elan related to the oral delivery platform developed within the Orasense collaboration and to ISIS 14803, Isis' antisense drug for the treatment of the hepatitis C virus, which is currently in Phase 2 clinical trials for the treatment of hepatitis C and was the focus of the HepaSense collaboration. In connection with this agreement, Elan transferred its shares of Isis Series B preferred stock to a third party. Immediately upon transfer, these shares converted into 1,055,502 shares of Isis common stock, eliminating the 5% in-kind dividend, thereby reducing future dilution of approximately 86,000 shares of Isis common stock. Isis also cancelled a warrant Elan held to purchase 14,881 shares of Isis common stock. In addition, a warrant Elan held to purchase 215,000 shares of Isis common stock expired unexercised in April 2004.

4. Strategic Alliances

Eli Lilly and Company

In September 2004, Eli Lilly and Company ("Lilly") licensed from Isis LY2275796. This second-generation antisense anti-cancer drug candidate targets eukaryotic initiation factor-4E (eIF-4E), a protein involved in tumor progression, angiogenesis and metastases. Isis earned a $750,000 payment from Lilly for the license.

Eyetech Pharmaceuticals, Inc.

In June 2004, Isis recorded $1.0 million in licensing revenue from Eyetech Pharmaceuticals, Inc. ("Eyetech") related to a milestone associated with the filing of a New Drug Application with the U.S. Food and Drug Administration ("FDA") for Macugen™ for the treatment of wet age-related macular degeneration. Macugen is a non-antisense oligonucleotide (aptamer). In 2002, Eyetech licensed from Isis specific patents necessary to develop, manufacture and commercialize Macugen. Under the terms of the agreement, Isis may earn additional milestone and royalty payments from Eyetech.

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.

In March 2004, Isis recorded $5.0 million in licensing revenue from this strategic alliance. As of September 30, 2004, Alnylam had paid $3.0 million of this fee to Isis. The remaining $2.0 million is due and payable to Isis in January 2005, and is reflected in contracts receivable on the accompanying condensed consolidated balance sheet as of September 30, 2004.

In June 2004, Isis recorded $500,000 in licensing revenue from Alnylam related to Alnylam's recently established alliance with Merck to develop and commercialize RNAi therapeutics for ocular diseases.

As part of its strategic alliance with Alnylam, Isis also made a $10.0 million equity investment in Alnylam.

In September 2004, Isis recorded a non-cash loss on investment of $5.0 million related to the impairment of the company's equity investment in Alnylam. The impairment reflects the decrease in the market value of Alnylam's stock, which Isis believes is a result of the current financial market conditions related to biotechnology companies.

5. Government Contracts

In September 2004, Isis was granted three government contracts valued at up to $10.0 million from the National Institute of Allergy and Infectious Diseases ("NIAID"), the Federal Bureau of Investigation ("FBI"), and an undisclosed government agency for the continued development of its TIGER biosensor technology.

Under the NIAID award, Isis will develop an application to use its TIGER technology to assess the safety of investigational vaccines and the components used for the manufacturing of biological products by identifying foreign infectious organisms that may be present. Under the FBI award, Isis will continue ongoing development of a microbial agent database.

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").

6. 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.

Revenue from significant partners as a percentage of total revenue was as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2004	2003	2004	2003
Partner A	47%	50%	33%	67%
Partner B	20%	24%	22%	16%
Partner C	13%	—%	4%	—%
Partner D	—%	—%	18%	—%

For the three and nine months ended September 30, 2004, Isis derived approximately 27% and 31%, respectively, of its revenue directly or indirectly from agencies of the U.S. Government. For the three and nine months ended September 30, 2003, Isis derived approximately 26% and 19%, respectively, of its revenue directly or indirectly from agencies of the U.S. Government.

Contract receivables from four significant partners comprised approximately 42%, 18%, 15% and 13% of contract receivables at September 30, 2004. Contract receivables from a single partner comprised approximately 49% of contract receivables at December 31, 2003.

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, the financial position of Isis Pharmaceuticals, 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 24 of this Report. As a result, you are cautioned not to 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 12 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, 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 first Phase III clinical trial of Affinitak to treat patients with non-small cell lung cancer, or NSCLC, 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 October 2004, we reported the results of a second Phase III clinical trial of Affinitak in combination with Gemzar® and cisplatin in patients with NSCLC. Findings from this trial, which was sponsored by Lilly, were similar to the results of the initial Isis-sponsored Phase III study of Affinitak for NSCLC. In this second study, patients in both treatment arms, those receiving Affinitak along with Gemzar and cisplatin and those receiving the chemotherapy alone, experienced equivalent median survival, the primary endpoint of the trial, of approximately 10 months. The addition of Affinitak to Gemzar and cisplatin was adequately tolerated. The safety profile of Affinitak in combination with the chemotherapy regimen was consistent with that observed in the previous Phase III trial. Although no final decision has been reached, given the outcome of both Phase III trials, additional investment in Affinitak is unlikely.

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. In addition, we are conducting two Phase II studies of alicaforsen in patients with ulcerative colitis. We plan to report data from these clinical trials by the end of 2004.

In August 2004, we announced that we are accelerating development of the oral formulation of ISIS 104838 for the treatment of rheumatoid arthritis, or RA, and that we plan to initiate a Phase II trial outside the U.S. comparing the oral and subcutaneous formulations of ISIS 104838 in patients with RA. Prior to initiating oral studies, we will

conduct preclinical safety studies to evaluate the safety of oral dosing, to support longer dosing and to reevaluate high dose toxicities and recovery from them. These studies are required to support further clinical trials in the U.S.

In addition to our Phase III trials for Affinitak and alicaforsen for Crohn's, and our Phase II trials for ISIS 104838 for RA, alicaforsen for ulcerative colitis, ISIS 113715 for diabetes, and ISIS 14803 for hepatitis C, we also have three drugs in Phase I clinical development and three drugs in preclinical development.

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.

Our TIGER program is sponsored by the Defense Advanced Research Projects Agency, or DARPA, under a subcontract from San Diego-based Science Applications International Corporation, or SAIC for bio-weapons defense. Our TIGER program is also funded by the Centers for Disease Control and Prevention, or CDC, for epidemiological surveillance applications, the Federal Bureau of Investigation, or FBI, for the development of a microbial agent database, and most recently by the National Institute of Allergy and Infectious Diseases, or NIAID, part of the National Institutes of Health, for biological products screening. The development of these various applications significantly broadens and enhances TIGER's commercial value and opportunity in the government, research instrument, and medical and diagnostic markets.

Under the NIAID award, we will develop an application to use our TIGER technology to assess the safety of investigational vaccines and the components used for the manufacturing of biological products by identifying foreign infectious organisms that may be present. Currently, there are few tests available that can specifically assess particular safety issues that are unique to cell substrates used in vaccine manufacturing, such as the identification of unknown or novel microbes that have the potential to contaminate vaccine cell lines and substrates. The TIGER biosensor has the potential to simultaneously identify a broad array of infectious agents, including previously unknown and newly emerging organisms that might be contaminating such cell substrates.

In October 2004, our Ibis program was granted three new government contracts, including the NIAID award, valued at up to $10.0 million for the continued development of our TIGER biosensor technology. Together with prior awards, we have received grants and contracts for up to $65.0 million in funding from agencies of the U.S. Government, including DARPA, the CDC, the National Institutes of Health, or NIH, the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID, and the U.S. Navy, and the FBI, among others.

We have a broad patent portfolio covering our technologies. We own or exclusively license more than 1,400 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 $42.0 million in license and royalty fees related to our patent portfolio.

We entered into a patent license agreement with Dharmacon, a wholly owned subsidiary of Fisher Scientific International, Inc. As an innovator in RNA-based drug discovery and development, our patent portfolio covers numerous aspects of antisense relevant to RNAi including specific chemical modifications of oliglionucleotides being used to create RNAi therapeutics for use in animals and humans. In order to sell chemically modified RNA for research purposes, Dharmacon, a leading global provider of innovative RNA research products, licensed from us certain chemistry and method-of-use patents in return for an upfront licensing fee and royalties on reagent sales. Through this agreement, we are able to provide access to our state-of-the-art technology to a wide array of academic labs, research institutes and companies practicing this technology while participating financially in Dharmacon's success.

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, Amgen, Antisense Therapeutics, Ltd., and OncoGenex Technologies, Inc., 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 and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of proper valuation of inventory;
- Determination of appropriate cost estimates for unbilled preclinical studies and clinical development activities; 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, or SAB No. 101, *Revenue Recognition in Financial Statements*, SAB 104, *Revenue Recognition*, and Emerging Issue Task Force, or EITF, No. 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables*.

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

We often enter into collaborations where we receive non-refundable 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 September 30, 2004, we had drawn down $90.0 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 often enter into revenue arrangements that contain multiple deliverables. In these cases, we recognize revenue from each element of the arrangement as long as we are able to determine a separate value for each element, we have completed our obligation to deliver or perform on that element and we are reasonably assured of collecting the resulting receivable.

Valuation of Investments in Marketable Securities

We account for our investments in marketable securities in accordance with current accounting rules as set forth by Statement of Financial Accounting Standards, or SFAS, No.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 on investments 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. During the third quarter of 2004, we recorded a non-cash loss on investments of $5.1 million principally related to the impairment of our equity investment in Alnylam. The impairment reflects the decrease in the market value of Alnylam's stock, which we believe is primarily a result of current financial market conditions related to biotechnology companies. The impairment does not reflect any change in our confidence that Alnylam will continue to be the center of excellence in RNAi or in our belief that the combination of our intellectual property and development expertise and Alnylam's intellectual property and research expertise in RNAi therapeutics will make significant progress in developing promising RNAi drugs.

Valuation of Long-Lived Assets

We assess the value of our long-lived assets, which include property and equipment, patent costs, and licenses acquired from third parties, under the provisions set forth by SFAS No. 144, *Accounting for the Impairment or Disposal of Long-Lived Assets*, or SFAS No. 144. We evaluate our long-lived assets for impairment on at least a quarterly basis. During this process, we review our property and equipment listings, pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties. To determine if any impairment is present, we consider the following, among other factors:

- Evidence of decreases in market value;
- Changes in the extent or manner in which we use an asset;
- Adverse changes in legal factors or in the business climate that would affect the value of an asset;
- An adverse action or assessment by a regulator;
- An accumulation of costs significantly in excess of amounts originally expected to acquire or construct an asset;
- Current period operating or cash flow loss combined with a history of operating or cash flow losses associated with an asset used for the purpose of producing revenue; and
- Challenges or potential challenges to our existing patents, the likelihood of applications being issued and

the scope of our issued patents.

In the event that we determine that impairment exists where we had previously determined that it did not exist, we may need to make a material adjustment to our condensed consolidated financial statements. To date, we have experienced no significant impairment of our long-lived assets.

Valuation of Inventory

We include in inventory material costs and related manufacturing costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. In the second quarter of 2003, we reduced the carrying value of our raw materials related to Affinitak™ to zero.

Estimated Liability for Clinical Development Costs

We maintain accrued liabilities related to unbilled costs for ongoing preclinical studies and clinical trials. These costs primarily relate to third-party clinical management costs, laboratory costs, toxicology studies and investigator grants, among other costs. We have multiple drugs in concurrent preclinical studies and clinical trials at several clinical sites throughout the world. We expect that at any given time we will have liabilities outstanding for our preclinical and clinical development costs related to products or services for which our service providers have not yet billed us. In order to ensure that we have adequately provided for ongoing preclinical and clinical development costs during the period in which we incur such costs, we maintain an accrual to cover these costs. We update our estimate for this accrual on at least a quarterly basis. The assessment of these costs is a subjective process that requires judgment. The ultimate settlement of these costs may differ materially from the amounts we have accrued in our condensed consolidated financial statements.

Valuation Allowance for Net Deferred Tax Asset

Isis recorded a valuation allowance to offset the net deferred tax assets because we are uncertain that we will realize these net tax assets. When and if circumstances warrant, we will assess the likelihood that our net deferred tax assets will more likely than not be recovered from future taxable income and

record an appropriate reversal to the valuation allowance. Because we have had net operating losses since inception, we have established a 100% valuation allowance for our net deferred tax asset.

Results of Operations

Revenue

Our total revenue for the three and nine months ended September 30, 2004 was $9.1 million and $31.2 million, respectively, compared to $11.3 million and $40.3 million for the same periods in 2003. Our revenue fluctuates from period-to-period based on the nature and timing of license fees and milestones earned, and other deliverables under agreements with partners. 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.

Under the category research and development revenue under collaborative agreements, we earned revenue of $9.1 million and $24.3 million for the three and nine months ended September 30, 2004, respectively, compared to $11.3 million and $39.9 million for the same periods in 2003. The decrease reflects the completion of Isis' Phase III clinical trial of Affinitak and an associated reduction in revenue, offset in part by increased revenue from our TIGER biosensor program, our strategic alliance with Alnylam and our research collaboration with Lilly, which included

$750,000 in revenue earned from Lilly in the third quarter of 2004 for the license of LY2275796, a second generation antisense anti-cancer drug candidate for clinical development.

Our revenue from licensing activities and royalties was $38,000 and $7.0 million, respectively for the three and nine months ended September 30, 2004, respectively, compared with $31,000 and $347,000 for the same periods in 2003. The increase for the nine months ended September 30, 2004 reflects $5.5 million we earned under our strategic alliance with Alnylam, and a $1.0 million milestone earned from Eyetech Pharmaceuticals, Inc. associated with Eyetech's filing of a New Drug Application, or NDA, with the U.S. Food and Drug Administration, or FDA, for Macugen™ for the treatment of wet age-related macular degeneration, or AMD.

Operating Expenses

Total operating expenses for the three and nine months ended September 30, 2004 were $31.5 million and $97.3 million, respectively, compared to $30.4 million and $97.8 million for the same periods in 2003. The changes were primarily due to non-cash compensation benefit due to variable accounting for stock options, and by increases in research and development and general and administrative expenses as we describe in the following paragraphs. In addition, we incurred restructuring costs of $1.8 million in 2003, and have incurred no such charges to date in 2004. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude compensation related to stock options from operating expenses because it is based on the variability of our stock price rather than operations, and to exclude restructuring activities because the costs are directly related to isolated events.

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 and nine months ended September 30, 2004, we incurred total research and development expenses of $29.6 million and $90.5 million, respectively, compared to $27.4 million and $87.8 million for the same periods in 2003. The increases were due primarily to increased spending to support our TIGER biosensor program, partially offset by planned expense reductions in other parts of the company that began in the second quarter of 2003.

Antisense drug discovery costs for the three and nine months ended September 30, 2004 were $10.2 million and $28.5 million, respectively, compared to $8.7 million and $27.9 million for the same periods in 2003. The increases of $1.5 million and $600,000 for the three and nine months, respectively, were principally the result of costs associated with advancement of programs under our Lilly research collaboration and start-up costs related to our Singapore laboratory, offset by 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 $10.9 million and $33.6 million for the three and nine months ended September 30, 2004, respectively, compared to $11.1 million and $36.7 million for the same periods in 2003. The decrease of $3.1 million for the nine months ended September 30, 2004 was primarily due to the completion in 2003 of our Phase III trial of Affinitak, offset in part by increased clinical development expenses for other products in development. 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. For example, in the second quarter of 2004 we decided not to initiate additional studies of ISIS 104838 for the treatment of psoriasis. 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 12 drug candidates in various stages of development, including two drugs in Phase III clinical trials, Affinitak and alicaforsen for Crohn's disease. Our partners are developing, with our support, five drug candidates, which substantially reduces our development costs.

There were no expenditures related to Affinitak for the three and nine months ended September 30, 2004. Expenditures related to Affinitak for the three and nine months ended September 30, 2003 were $143,000 and $7.3

million, respectively. 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. In October 2004, we reported the results of a second Phase III clinical trial of Affinitak in combination with Gemzar® and cisplatin in patients with NSCLC. Findings from this trial, which was sponsored by Lilly, were similar to the results of the first Isis-sponsored Phase III study of Affinitak for NSCLC. Although no final decision has been reached, given the outcome of both Phase 3 trials, additional investment in Affinitak is unlikely.

We incurred development expenditures related to our second drug in Phase III trials, alicaforsen for Crohn's disease, of $1.2 million and $4.5 million for the three and nine months ended September 30, 2004, respectively, compared to $1.9 million and $5.5 million for the same periods in 2003. The decreasees of $700,000 and $1.0 million for the three and nine months, respectively, are consistent with our ongoing development efforts for alicaforsen. We plan to report data on our Phase III trials of alicaforsen for Crohn's disease by the end of 2004.

We incurred expenses related to our other products in development of $8.3 million and $23.6 million for the three and nine months ended September 30, 2004, respectively, compared to $8.4 million and $22.1 million for the same period in 2003. The increase in the nine months ended September 30, 2004, compared to the same period in 2003, was 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 other products in the early stages of development.

Our Ibis program expenses for the three and nine months ended September 30, 2004 were $2.1 million and $8.6 million, respectively, compared to $1.8 million and $6.8 million for the same periods in 2003. The increases were the result of our performance under our contracts with DARPA, USAMRIID, the CDC, and with various other government agencies, primarily in support of our TIGER biosensor program. We include in our Ibis program 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 and nine months ended September 30, 2004 were $6.4 million and $19.8 million, respectively, compared to $5.8 million and $16.5 million for the same periods in 2003. While we experienced decreases in direct research and development costs during the first three and nine 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 research and development activities.

General and administrative expenses for the three and nine months ended September 30, 2004 were $2.4 million and $7.4 million, respectively, compared to $2.1 million and $7.2 million for the same periods in 2003. The increases of $300,000 and $200,000 for the three and nine months ended September 30, 2004, respectively were primarily related to personnel, consulting, and outside services for finance, investor relations and business development activities as compared to the same periods in 2003.

Compensation benefit related to stock options for the three and nine months ended September 30, 2004 was $466,000 and $649,000 respectively, compared to compensation expense of $804,000 and $936,000 for the same periods in 2003. The changes in compensation expense (benefit) were primarily related to the effects of using variable accounting to account for 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, or APB, Opinion No. 25 and Financial Accounting Standards Board Interpretation, or FIN, No. 44.

Investment Income

Investment income for the three and nine months ended September 30, 2004 totaled $561,000 and $2.5 million, respectively, compared to $1.2 million and $4.0 million for the same periods in 2003. The decrease in investment income for the first three and nine months of 2004 over 2003 was primarily due to our lower average cash balance for the first three and nine months of 2004 compared to the first three and nine 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 and nine months ended September 30, 2004 totaled $5.8 million and $16.4 million, respectively, compared to $4.3 million and $13.7 million for the same periods in 2003. This increase was due to the effect of a higher debt balance as of September 30, 2004, compared to September 30, 2003 related to the loan to fund our Lilly research collaboration. 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.

Loss on Investments

For the nine months ended September 30, 2004, we incurred a non-cash loss on investments of $5.1 million principally related to the impairment of our equity investment in Alnylam compared to a non-cash loss on investments of $2.4 million related to the impairment of our equity investments in ATL and Hybridon for the same period in the prior year.

Net Loss Applicable to Common Stock

For the three and nine months ended September 30, 2004, we reported a net loss applicable to common stock of $32.7 million and $85.3 million, respectively, compared to a net loss applicable to common stock of $22.4 million and $70.1 million for the same periods in 2003. In June 2004, Isis entered into an agreement with a subsidiary of Elan Corporation, plc, ("Elan") to acquire Elan's minority interest in Orasense ™ and HepaSense ™. In connection with this agreement, Elan transferred its shares of Isis Series B preferred stock to a third party. Immediately upon transfer, these shares converted into 1,055,502 shares of Isis common stock, eliminating the 5% in-kind dividend. As a result of the agreement with Elan, our net loss applicable to common stock included zero and approximately $361,000 of accreted dividends on preferred stock for the three and nine months ended September 30, 2004, respectively, compared to $175,000 and $518,000 for the same periods in 2003.

The increases in net loss applicable to common stock for the three and nine months ended September 30, 2004 compared to the same periods in 2003 were primarily the result of a decrease in revenue, increase in operating expenses, decrease in interest income, and increase in interest expense as described previously. The net effect of these changes was offset in part by compensation benefit related to stock options. In addition, during the nine months ended September 30, 2003, we incurred a charge of $1.8 million related to restructuring activities. There were no restructuring charges incurred during the same period in 2004. For the nine months ended September 30, 2003 we incurred a non-cash loss on investments of $2.4 million related to the impairment of our investments in ATL and Hybridon. For the nine months ended September 30, 2004, we incurred a non-cash loss on investments of $5.1 million principally related to the impairment of our equity investment in Alnylam. The impairment reflects the decrease in the market value of Alnylam's stock, which we

believe is primarily a result of the current financial market conditions related to biotechnology companies. The impairment does not reflect any change in our confidence that Alnylam will continue to be the center of excellence in RNAi or in our belief that the combination of our intellectual property and development expertise and Alnylam's intellectual property and research expertise in RNAi therapeutics will make significant progress in developing promising RNAi drugs.

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 September 30, 2004, we have earned approximately $431.7 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 $592.4 million from the sale of equity securities. We have borrowed approximately $375.0 million under long-term debt arrangements to finance a portion of our operations.

As of September 30, 2004, we had cash, cash equivalents and short-term investments totaling $125.6 million, working capital of $116.5 million and a stockholders' deficit of $17.6 million. In comparison, we had cash, cash equivalents and short-term investments of $215.5 million, working capital of $194.0 million and stockholders' equity of $67.2 million as of December 31, 2003. Our $100.0 million Lilly research collaboration loan, of which $90.0 million was outstanding as of September 30, 2004, comes due in August 2005. We can repay this loan at our option in either cash or our common stock at a fixed conversion price of $40 per share. If we draw down the remaining amount available under the loan, we could repay the loan for 2.5 million shares of our common stock. Accordingly, the outstanding balance on this loan has been classified as a long-term obligation in the current quarter. 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 September 30, 2004, our debt and other obligations totaled $254.3 million, compared to $250.6 million at December 31, 2003. Our debt and other obligations at September 30, 2004 included current and long-term deferred contract revenue of approximately $15.0 million and other contractual obligations. The increase in our debt and other obligations is primarily due to additional draw downs from the $100.0 million interest-free loan from Lilly, which we discounted to their present value by imputing interest on the amounts at 20% and accreting to their face value over their term by recording interest expense. The increase in debt was partially offset by the repayment in January of convertible partner debt from Boehringer Ingleheim International BmbH, or BI, of approximately $6.4 million, the payment of principal and interest related to our standard operating debt, and payments related to our capital leases. 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 September 30, 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 September 30, 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:

Contractual Obligations (selected balances described below)	Payments Due by Period (in thousands)				
	Total	Less than 1 year	1-3 years	3-5 years	After 5 years
Lilly Research Collaboration Loan	$ 90.0	$ 90.0	$ —	$ —	$ —
5 ½% Convertible Subordinated Notes	$ 125.0	$ —	$ —	$ 125.0	$ —
Standard Operating Debt	$ 33.7	$ 6.3	$ 18.7	$ 8.7	$ —
Capital Lease Obligations	$ 5.6	$ 3.7	$ 1.9	$ —	$ —
Operating Leases	$ 10.3	$ 2.8	$ 5.0	$ 1.9	$ 0.6

Our contractual obligations consist primarily of our publicly traded convertible debt and Lilly research collaboration loan. We can repay our Lilly research collaboration loan at our option in either cash or our common stock at a fixed conversion price of $40 per share. If we draw down the remaining amount available under the loan,

we could repay the loan for 2.5 million shares of our common stock. In addition, we also have standard operating debt, capital leases and other obligations. Our standard operating debt includes a 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 4.75% at September 30, 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 September 30, 2004 and December 31, 2003 was $27.6 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 September 30, 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 September 30, 2004, we had drawn down $90.0 million of the $100.0 million available. We discounted the $90.0 million loan to its present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We 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 given to us by Lilly 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. As of September 30, 2004, the balance in long-term obligations was $75.0 million and the balance in deferred revenue was $15.0 million.

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 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 that have not met the primary clinical end points in their initial Phase III studies.

In March 2003, we reported the results of a Phase III clinical trial of Affinitak in patients with late stage non-small cell lung cancer and in October 2004, we reported the results of a second similar phase III clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient enough to support an NDA filing. A similar result could occur with 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. In addition, although no final decision has been reached, given the outcome of both Phase III trials, additional investment in Affinitak is unlikely.

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 the two Affinitak trials or any future clinical trial failures could impair our ability to attract new collaborative partners. 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 require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of September 30, 2004, our accumulated losses were approximately $640.9 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, with reasonable assumptions for new sources of revenue and cash, we believe that our available cash, cash equivalents and short-term investments as of September 30, 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 products, or to license our drugs and 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 or revenue source.

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 or 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.

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 clinical trials 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 September 30, 2004, the market price of our common stock has ranged from $4.27 to $9.50 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 Eli Lilly and Company. These registration rights cover approximately 2.5 million shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these securities are converted and the holder exercises its 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.

Our business is subject to changing regulations for corporate governance and public disclosure that has increased both our costs and the risk of noncompliance.

We are evaluating our internal controls systems in order to allow management to report on, and our Registered Independent Public Accounting Firm to attest to, our internal controls, as required by Section 404 of the Sarbanes-Oxley Act. We are performing the system and process evaluation and testing required in an effort to comply with the management certification and auditor attestation requirements of Section 404. As a result, we are incurring additional expenses and a diversion of management's time. While we anticipate being able to fully implement the requirements relating to internal controls and all other aspects of Section 404 in a timely fashion, we cannot be

certain as to the timing of completion of our evaluation, testing and remediation actions or the impact of the same on our operations since there is no precedent available by which to measure compliance adequacy. If we are not able to implement the requirements of Section 404 in a timely manner or with adequate compliance, we might be subject to sanctions or investigation by regulatory authorities, such as the Securities and Exchange Commission, the Public Company Accounting Oversight Board, or PCAOB, or the NASDAQ Stock Exchange. Any such action could adversely affect our financial results and the market price of our common stock.

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 September 30, 2004. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 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.

We are conducting a detailed assessment of our internal controls as called for by the Sarbanes-Oxley Act of 2002. As a result of this assessment, we have identified what may be control deficiencies in our system of internal controls. As a result, we have established a remediation team to investigate these potential control deficiencies, and, where appropriate, to remediate them. We do not believe that identified potential control deficiencies in our system of internal controls qualify as significant deficiencies or material weaknesses, as defined by the PCAOB, Auditing Standard No. 2, "An Audit of Internal Control Over Financial Reporting Performed in Conjunction With an Audit of Financial Statements." As we complete the testing phase of our project, we will continue to validate potential control deficiencies, if any, and to assess whether or not they qualify as significant deficiencies or material weaknesses. Although we have made this project one of our top priorities, we can not be certain that we will successfully remediate all control deficiencies identified and validated before the end of our fiscal year, or that any remaining unresolved control deficiencies will not qualify as significant deficiencies or material weaknesses.

PART II — OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Not applicable

ITEM 2. UNREGISTERED SALES OF EQUITY 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

In October 2004, we modified our development agreement with RoboDesign International, Inc. dated November 12, 2003 to provide for the early delivery of a prototype TIGER 2.0 system so that we could test the system at our facilities. As part of the early delivery, we pre-paid RoboDesign a portion of the development fees for the prototype. The remainder of the development fees will be due in accordance with the terms of the original development agreement.

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.5	Development Agreement dated September 30, 2004 between Isis Pharmaceuticals, Inc. and the National Institute of Allergy and Infectious Diseases (with certain confidential information deleted).
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.

Isis Pharmaceuticals, Inc.
(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, M.D., Ph.D. Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	November 5, 2004
/s/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	November 5, 2004

Exhibit 10.5
Confidential Treatment Requested
Under 17 C.F.R. §§200.80(b)(4),
200.83 and 240.24b-2

ADB No. N01-AI-40100

OMB App-al 2700-0042

AWARD/CONTRACT	1. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 350)	RATING N/A	
2. CONTRACT *(Proc. Inst. Ident.)* NO. HHSN266200400100C	3. EFFECTIVE DATE September 30, 2004	4. REQUISITION/PURCHASE REQUEST/PROJECT NO. PRCB223	

5. ISSUED BY CODE I	6. ADMINISTERED BY *(If other than Item 6)* CODE
National Institutes of Health, DHHS NIAID, DEA, CMP, PRCB Room [***], MSC [***] 6700-B Rockledge Drive Bethesda, Maryland 20892-7612	PRCB-DMID RFP NIH-NIAID-DMID-04-22

7. NAME AND ADDRESS OF CONTRACTOR *(No. street, county* state *and ZIP Code)*	8. DELIVERY 0 FOB ORIGIN ® OTHER *(Seebe/ow)*
ISIS Pharmaceuticals Ibis Therapeutics Division 2292 Faraday Ave Carlsbad, California, 92008	9/ DISCOUNT FOR PROMPT PAYMENT N/A
	10. SUBMIT INVOICES ADDRESS SHOWN IN: ITEM Art. G.3.

CODE	FACILITY CODE			
11. SHIP TO/MARK FOR CODE	N/A	12. PAYMENT WILL BE MADE BY CODE		N/A
Article F.1.		See Article G.3.		
13. AUTHORITY FOR USING OTHER FULL AND OPEN COMPETITION: N/A 10 U.S.C. 2304(c)( ) 41 U.S.C. 253(c)( )		14. ACCOUNTING AND APPROPRIATION DATA EIN# 1330336973A1 SOC 25.55 CAN# 4-8460924 $2,489,423		

15A. ITEM NO.	15B. SUPPLIES/SERVICES	15C. UNIT PRICE	15D. AMOUNT	15E. UNIT PRICE	15F. AMOUNT
Title: Assessing Safety of Cell Substrates and Vaccine Components, Part		FY 04	[***]		[***]
E: Develop, characterize and validate assays for detection of novel or		FY 06	[***]		[***]
latent/occult adventitious agents in cell substrates		FY 07	[***]		[***]
Period: September 24, 2004 through September 23, 2009		FY 08	[***]		[***]
Contract Type: CPFF-Completion					
					$5,613,317

15G. TOTAL AMOUNT OF CONTRACT

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CONTRACTING OFFICER WILL COMPLETE ITEM 17 OR 18 AS APPLICABLE

17. ☒ CONTRACTOR'S NEGOTIATED AGREEMENT *(Contractor is required to sign this document and return* 2 copies to *issuing office.)*
Contractor agrees to furnish and deliver all items or perform all the services set forth or otherwise identified above and on any continuation sheets for the consideration stated herein. The rights and obligations of the parties to this contract shall be subject to and governed by the following documents: (a) this award/contract, (b) the solicitation, if any, and (c) such provisions, representations, certifications, and specifications, as are attached or incorporated by reference herein. *(Attachments are listed herein.)*

18.o AWARD *(Contractor is not required* to *sign this document.)* Your offer on Solicitation Number_____
including the additions or changes made by you which additions or changes are set forth in full above, is hereby accepted as to the items listed above and on any continuation sheets. This award consummates the contract which consists of the following documents: (a) the Government's solicitation and your offer, and (b) this award/contract. No further contractual document is necessary.

19A. NAME AND TITLE OF SIGNER *(Type or print)*

S˜F˜*fa*, t.tt_ay 'T C2o KE

Gc=cJ

20A NAME OF CONTRACTING OFFICER
Carl A. Newman
Contracting Officer, PRCB, CMP, NIAID, NIH, DHHS

19B. NAME OF CONTRACTOR

(Signature of person authorized to sign)

9C. DATE SIGNED

20B. U ED STATES OF AMERICA

B Y

(Signature of Contracting Officer)

20C. DATE SIGNED

NSN 7540-01-152-8069
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STANDARD FORM 26 (REV. 4-85)
Prescribed by GSA
FAR (48 CFR) 53.214(a)

PART I - THE SCHEDULE

SECTION B - SUPPLIES OR SERVICES AND PRICES/COSTS

ARTICLE B.1. BRIEF DESCRIPTION OF SUPPLIES OR SERVICES

The focus of this contract is to develop methods to assess current and future safety concerns that arise regarding vaccines and vaccine manufacturing and/or formulation. The contractor shall develop, characterize and validate assays for detection of novel or latent/occult adventitious agents.

ARTICLE B.2. ESTIMATED COST AND FIXED FEE

a. The estimated cost of this contract is [***].

b. The fixed fee for this contract is [***]. The fixed fee shall be paid in installments based on the percentage of completion of work, as determined by the Contracting Officer, and subject to the withholding provisions of the clauses ALLOWABLE COST AND PAYMENT and FIXED FEE referenced in the General Clause Listing in Part II, ARTICLE 1.1. of this contract. Payment of fixed fee shall not be made in less than monthly increments.

c. The Government's obligation, represented by the sum of the estimated cost plus the fixed fee, is $5,613,317.

d. Total funds currently available for payment and allotted to this contract are [***]. The estimated cost is [***] and the fixed fee is [***]. For further provisions on funding see the LIMITATION OF FUNDS clause referenced in Part II, ARTICLE 1.3. Authorized Substitutions of Clauses.

e. It is estimated that the amount currently allotted will cover performance of the contract through January 31, 2007.

f. The Contracting Officer may allot additional funds to the contract without the concurrence of the Contractor.

g. Increments to be allotted to this contract are estimated as follows:

Fiscal Year	Total Cost Excluding Fee	Fixed Fee	Amount
FY 04	[***]	[***]	[***]
FY 06	[***]	[***]	[***]
FY 07	[***]	[***]	[***]
FY 08	[***]	[***]	[***]
Total	**[***]**	**[***]**	**$ 5,613,317**

ARTICLE B.3. PROVISIONS APPLICABLE TO DIRECT COSTS

a. **Items Unallowable Unless Otherwise Provided**

Notwithstanding the clauses, ALLOWABLE COST AND PAYMENT, and FIXED FEE, incorporated in this contract, unless authorized in writing by the Contracting Officer, the costs of the following items or activities shall be unallowable as direct costs:

(1) Acquisition, by purchase or lease, of any interest in real property;
(2) Special rearrangement or alteration of facilities;
(3) Purchase or lease of **any** item of general purpose office furniture or office equipment regardless of dollar value. (General purpose equipment is defined as any items of personal property which are usable for purposes other than research, such as office equipment and furnishings, pocket calculators, etc.);
(4) Travel to attend general scientific meetings;
(5) Foreign travel - See paragraph b.2. below;
(6) Consultant costs;
(7) Subcontracts;
(8) Patient care costs;
(9) Accountable Government property (defined as both real and personal property with an acquisition cost of $1,000 or more and a life expectancy of more than two years) and "sensitive items" (defined and listed in the Contractor's Guide for Control of Government Property, 1990), regardless of acquisition value.

b. **Travel Costs**

Domestic Travel

(1) (a) Total expenditures for domestic travel (transportation, lodging, subsistence, and incidental expenses) incurred in direct performance of this contract shall not exceed [***] without the prior written approval of the Contracting Officer. The Contractor is authorized to travel to attend programmatic meetings.
(b) The Contractor shall invoice and be reimbursed for all travel costs in accordance with Federal Acquisition Regulations (FAR) 31.205-46.

(2) Foreign Travel

Requests for foreign travel must be submitted at least six weeks in advance and shall contain the following: (a) meeting(s) and place(s) to be visited, with costs and dates; (b) name(s) and title(s) of Contractor personnel to travel and their functions in the contract project; (c) contract purposes to be served by the travel; (d) how travel of contractor personnel will benefit and contribute to accomplishing the contract project, or will otherwise justify the expenditure of NIH contract funds; (e) how such advantages justify the costs for travel and

absence from the project of more than one person if such are suggested; and (f) what additional functions may be performed by the travelers to accomplish other purposes of the contract and thus further benefit the project.

ARTICLE B.4. ADVANCE UNDERSTANDINGS

Other provisions of this contract notwithstanding, approval of the following items within the limits set forth is hereby granted without further authorization from the Contracting Officer.

a. **Invoices - Cost and Personnel Reporting, and Variances from the Negotiated Budget**

(1) The contractor agrees to provide a detailed breakdown on invoices of the following cost categories:

(a) Direct Labor - List individuals by name, title/position, hourly/annual rate, level of effort, and amount claimed.
(b) Fringe Benefits - Cite rate and amount
(c) Overhead - Cite rate and amount
(d) Materials & Supplies - Include detailed breakdown when total amount is over $1,000.
(e) Travel - Identify travelers, dates, destination, purpose of trip, and amount. Cite COA, if appropriate. List separately, domestic travel, general scientific meeting travel, and foreign travel.
(f) Consultant Fees - Identify individuals and amounts.
(g) Subcontracts - Attach subcontractor invoice(s).
(h) Equipment - Cite authorization and amount.
(i) G&A - Cite rate and amount.
(j) Total Cost
(k) Fixed Fee
(1) Total CPFF

Monthly invoices must include the cumulative total expenses to date, adjusted (as applicable) to show any amounts suspended by the Government.

(2) The contractor agrees to immediately notify the contracting officer in writing if there is an anticipated overrun (any amount) or unexpended balance (greater than [***] percent) of the amount allotted to the contract, and the reasons for the variance. Also refer to the requirements of the Limitation of Funds and Limitation of Cost Clauses in the contract.

b. **Indirect Costs Rates**

The Contractor may apply the following provisional indirect rates for the initial [***] days of the contract: Fringe Benefit at [***], Overhead at [***] and G&A at [***]. Final rates will apply once the cognizant Government audit agency completes the audit and

provides an indirect rate agreement.

c. **Consultants**

Consultant fee to be paid to the following individual for the period [***] through [***]:

Name	Fiscal Year	Rate Per Hour	Number of Hours	Total Cost Excluding Travel Not to Exceed
[***] Ph.D.	[***]	[***]	[***]	[***]
[***] Ph.D.	[***]	[***]	[***]	[***]
[***] Ph.D.	[***]	[***]	[***]	[***]
[***] Ph.D.	[***]	[***]	[***]	[***]
[***] Ph.D.	[***]	[***]	[***]	[***]

d. **Government Property**

Of the total contract value, [***] is hereby set aside for the purchase of the equipment identified in ARTICLE G.5.c., Contractor- Acquired Government Property - Schedule IA. Schedule I-A is provided as Attachment 6 to this contract. A variance of [***] of each cost per item shown in the attachment is authorized without further action by the Contracting Officer. Any substitutions of the listed equipment shall require prior written approval of the Contracting Officer.

e. **Correspondence Procedures**

To promote timely and effective administration, correspondence (except for financial reports, technical progress reports/other deliverables) submitted under this contract shall be subject to the following procedures:

1. Technical correspondence shall be addressed to the Project Officer with an information copy of the basic correspondence to the Contracting Officer. (As used herein, technical correspondence excludes correspondence which proposes deviations from or modifications of contract requirements, terms or conditions.)

2. Other correspondence shall be addressed to the Contracting Officer, with an information copy of the basic correspondence to the Project Officer.

3. Subject Line(s). All correspondence shall contain a subject line commencing with the contract number as illustrated below:

SUBJECT: Contract No. HHSN266200400100C
ADB Contract No. NO1-AI-40100

Request for Approval of

f. **Confidential Treatment Of Sensitive Information**

The Contractor shall guarantee strict confidentiality of the information/data that it is provided by the Government during the performance of the contract. The Government has determined that the information/data that the Contractor will be provided during the performance of the contract is of a sensitive nature.

Disclosure of the information/data, in whole or in part, by the Contractor can only be made after the Contractor receives prior written approval from the Contracting Officer. Whenever the Contractor is uncertain with regard to the proper handling of information/data under the contract, the Contractor shall obtain a written determination from the Contracting Officer.

SECTION C - WORK STATEMENT

ARTICLE C.1. STATEMENT OF WORK

a. Independently and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government as needed to perform the Statement of Work, SECTION J, ATTACHMENT 1, dated September 10, attached hereto and made a part of this contract.

ARTICLE C.2. REPORTING REQUIREMENTS

In addition to those reports required by the other terms of this contract, the Contractor shall prepare and submit the following reports in the manner stated below and in accordance with Article F. 1. Deliveries of this contract. The Contractor shall submit electronic and hard copy versions of each report.

All reports shall contain a title page that includes:

Contract number and title
Contract Project Officer
Type of report (Quarterly, Annual, or Final)
Period of performance being reported
Contractor's name and address
Author(s)
Date of Submission

I. SEMI-ANNUAL TECHNICAL PROGRESS REPORT

By the thirtieth calendar day of the month following the end of each six month period, the Contractor shall submit three (3) copies of a semi-annual Technical Progress Report, comprising two (2) copies [one (1) hard copy and one (1) electronic copy] to the Project Officer and one (1) hard copy to the Contracting Officer. The semi-Annual Report shall be factual and concise and consist of the following:

a. Section I: An introduction covering the purpose and scope of the contract effort.

b. Section II: Brief overview of all work performed on development and validation in the previous six months.

c. Section III: Description of overall progress, plus a separate description for each task or segment of work on which effort was expended during the reporting period. The description for each task will include:

i. Pertinent data and/or graphs in sufficient detail to explain any significant results achieved and preliminary conclusions resulting from analysis and scientific evaluation of data accumulated to date under the project;
ii. Any scientific, technical, or other problems/difficulties encountered;
iii. Brief description of planned work for the following six month period;
iv. Any recommendations for the modification, expansion, curtailment and/or termination of development/validation of the assay.

d. Section IV: An anticipated work plan for the following six months.

e. Section V: A description of all impediments in carrying out the work tasks, whether affecting performance or costs, and methods implemented to overcome impediments. If impediments are ongoing, report should include recommendations for their resolutions.

f. Semi-annual Technical Progress Reports are not due for periods in which an annual or final report is due.

II. ANNUAL REPORT

By the thirtieth calendar day after the anniversary date of the contract, the Contractor shall submit three (3) copies of an Annual Technical Progress Report, comprising two (2) copies to the Project Officer [one (1) hard copy and one (1) electronic copy] and one (1) hard copy to the Contracting Officer. Such reports shall detail, document, and summarize the results of the entire contract work for the period covered.

a. Section I: An introduction covering the purpose and scope of the contract effort.

b. Section II: Brief overview of all work performed since the last annual report, including progress on meeting objectives identified in the previous annual report.

c. Section III: Description of overall progress, plus a separate description for each task or segment of work on which effort was expended during the report period. The description for each task will include:

i. Pertinent data and/or graphs in sufficient detail to explain any significant results achieved and preliminary conclusions resulting from analysis and scientific evaluation of data accumulated to date under the project;
ii. Any scientific, technical, or other problems/difficulties encountered;
iii. Brief description of planned work for the following six month period;
iv. Any recommendations for the modification, expansion, curtailment and/or termination of development/validation of the assay.

d. Section IV: Objectives for the upcoming 12-month period, and an anticipated work plan that will allow the objectives to be met.

e. Section V: A description of all impediments in carrying out the work tasks, whether affecting performance or costs, and methods implemented to overcome impediments. If impediments are ongoing, report should include recommendations for their resolutions.

f. An annual report will not be required for the period when the final report is due.

III. FINAL REPORT

At the completion of the contract period, the Contractor shall submit the Final Technical Report summarizing the results for the entire contract work for the complete performance period. A draft of the Final Report shall be submitted 30 calendar days prior to the expiration date of the contract. Project Officer will have 14 calendar days from date of receipt to review and comment on the draft final report. The Final Report shall be submitted by the expiration date of the contract and shall be submitted in place of the last Annual Report. The Contractor shall submit three (3) copies of the Final Report, comprising two (2) copies to the Project Officer [one (1) hard copy and one (1) electronic copy] and one (1) hard copy to the Contracting Officer.

The Final Report shall include:

a. A detailed description of the results of all work conducted under this contract. Description should be in sufficient detail to explain comprehensively the results achieved.

b. Conclusions regarding work performed and recommendations for continued development of assays.

c. Recommendations for new assays/approaches that could be investigated to achieve the aims laid out in the contract.

d. Final cost of work performed on each assay.

e. A discussion of problems and obstacles encountered while performing assay development and validation. Discussion should include both technical and programmatic issues, and should detail methods (both successful and unsuccessful) that were used to overcome the problems and obstacles, and recommendations for improvements.

IV. OTHER DELIVERABLES

1. Draft assay development protocols will be delivered to the project officer for review and approval at least 30 calendar days prior to planned study initiation. Final assay development protocols will be delivered to the project officer at least 7 calendar days prior to planned study initiation.

2. Draft assay validation plans will be delivered to the project officer for review and approval at least 45 calendar days prior to planned study initiation. Validation plans will include the following information/sections: Cover page, table of contents, purpose, study objective, responsibilities, definitions, summary of completed studies, study description, sample description, materials and supplies, equipment information, test methods, Standard Operating Procedures (SOPs), test protocol (Test functions describing each validation parameter, how it will be tested, and the acceptance criteria), data handling and analysis, and report requirements. Final assay validation protocols will be delivered to the project officer at least 7 calendar days prior to planned study initiation.

3. Draft and Final study reports for all implemented studies, including assay development, assay validation, and assays that were terminated/curtailed prior to completion of assay development or assay validation. Draft reports are due 60 calendar days following completion of validation studies, or termination/curtailment of studies. Report will include the following sections/information: Cover page, table of contents, abstract, methods and materials, results (which will include data analysis and compilation of data into figures and/or tables as requested by the NIAID Project Officer), conclusions, and appendices. For assay validation study reports, the `results' section of the study report will be divided into subsections, with each subsection dedicated to one of the validation parameters (based on the test protocol). Final study reports are due 30 calendar days after the contractor has received comments from the NIAD Project Officer.

4. Contractor shall provide data, reports, and other information related to this Contract as requested by the Project Officer.

V. TRANSITION PLAN

Twelve months prior to the completion date of this contract, a transition plan shall be submitted by the Contractor to the NIAID Project Officer for review and approval. The transition plan will be a detailed plan for the orderly transition of contract-related material to a successor contractor or the government. The transition plan will include a detailed description of the methods and procedures for the transition, the timeline for preparation and delivery of various materials, and the mechanism(s) to be used to provide access to all data generated under this contract.

ARTICLE C.3. INVENTION REPORTING REQUIREMENT

All reports and documentation required by FAR Clause 52.227-11 including, but not limited to, the invention disclosure report, the confirmatory license, and the government support certification, shall be directed to the Extramural Inventions and Technology Resources Branch, OPERA, NIH, 6705 Rockledge Drive, Room [***], MSC [***], Bethesda, Maryland 208927980 (Telephone: 301-435-1986). In addition, one copy of an annual utilization report, and a copy of the final invention statement, shall be submitted to the Contracting Officer. The final invention statement (see FAR 27.303(a)(2)(ii)) shall be submitted to the Contracting Officer on the expiration date of the contract.

The annual utilization report shall be submitted in accordance with ARTICLE F. 1. DELIVERIES of this contract. The final invention statement (see FAR 27.303(a)(2)(ii)) shall be submitted on the expiration date of the contract to the following address:

Contracting Officer
PRCB, CMP, DEA, NIAID, NIH, DHHS
Room [***]
6700-B Rockledge Drive, MSC [***]
Bethesda, MD 20892-7612

If no invention is disclosed or no activity has occurred on a previously disclosed invention during the applicable reporting period, a negative report shall be submitted to the Contracting Officer at the address listed above.

To assist contractors in complying with invention reporting requirements of the clause, the NIH has developed "Interagency Edison," an electronic invention reporting system. Use of Interagency Edison is encouraged as it streamlines the reporting process and greatly reduces paperwork. Access to the system is through a secure interactive Web site to ensure that all information submitted is protected. Interagency Edison and information relating to the capabilities of the system can be obtained from the Web (http://www.iedison.gov), or by contacting the Extramural Inventions and Technology Resources Branch, OPERA, NIH.

SECTION D - PACKAGING, MARKING AND SHIPPING

All deliverables required under this contract shall be packaged, marked and shipped in

accordance with Government specifications. At a minimum, all deliverables shall be marked with the contract number and contractor name. The Contractor shall guarantee that all required materials shall be delivered in immediate usable and acceptable condition.

SECTION E - INSPECTION AND ACCEPTANCE

a. The Contracting Officer or the duly authorized representative will perform inspection and acceptance of materials and services to be provided.

b. For the purpose of this SECTION the Project Officer identified in ARTICLE G.1. is the authorized representative of the Contracting Officer.

c. Inspection and acceptance will be performed at the address listed for the Project Officer in Section G, Article G. 1. Acceptance may be presumed unless otherwise indicated in writing by the Contracting Officer or the duly authorized representative within 30 days of receipt.

d. This contract incorporates the following clause by reference, with the same force and effect as if it were given in full text. Upon request, the Contracting Officer will make its full text available.

FAR Clause No. 52.246-9, INSPECTION OF RESEARCH AND DEVELOPMENT (SHORT FORM) (APRIL 1984).

SECTION F - DELIVERIES OR PERFORMANCE

ARTICLE F.1. DELIVERIES

Satisfactory performance of this contract shall be deemed to occur upon performance of the work described in Article C. 1. and upon delivery and acceptance by the Contracting Officer, or the duly authorized representative, of the following items in accordance with the stated delivery schedule:

a. The items specified below as described in SECTION C, ARTICLE C.2. will be required to be delivered F.O.B. Destination as set forth in FAR 52.247-35, F.O.B. DESTINATION, WITHIN CONSIGNEES PREMISES (APRIL 1984), and in accordance with and by the date(s) specified below:

Report Distribution

Deliverable	No. of Copies	Addressee/Distribution	Due Dates	
Semi-Annual Progress Reports		Project Officer ORA, DMID, NIAID, NIH, DHHS Room [***], MSC [***] 6610 Rockledge Drive Bethesda, MD 20892-6603	The 30th of the end of performance	the month following each semi-annual period.
	1	Contracting Officer PRCB,CMP, DEA, NIAID, NIH, DHHS 6700-B Rockledge Drive Room [***], MSC [***] Bethesda, MD 20892-7612		

Annual Progress Reports	2	Project Officer, as above.	The 30th of the month following the yearly anniversary date of the contract.
	1	Contracting Officer, as above.	
Draft Final Report	2	Project Officer, as above.	30 days prior to completion date of the contract.
Final Report	2	Project Officer, as above.	Completion date of the contract.
	1	Contracting Officer, as above.	
Other Deliverables	3	TBD	TBD
Invention Reporting	1	Contracting Officer, as above.	The 30th of the month following the yearly anniversary date of the contract.
Transition Report	2	Project Officer, as above.	12 months prior to completion date of the contract.
	1	Contracting Officer, as above.	

ARTICLE F.2. CLAUSES INCORPORATED BY REFERENCE, FAR 52.252-2 (FEBRUARY 1998)

This contract incorporates the following clause by reference, with the same force and effect as if it were given in full text. Upon request, the Contracting Officer will make its full text available. Also, the full text of a clause may be accessed electronically at this address: http://www.arnet.gov/far/.

FEDERAL ACQUISITION REGULATION (48 CFR CHAPTER 1) CLAUSE:

52.242-15, Stop Work Order (AUGUST 1989) with ALTERNATE I (APRIL 1984).

SECTION G - CONTRACT ADMINISTRATION DATA

ARTICLE G.1. PROJECT OFFICER

The following Project Officer will represent the Government for the purpose of this contract:

[***], Ph.D.
Project Officer, Office of Regulatory Affairs Division of Microbiology and Infectious Diseases NIAID, NIH, DHHS
6610 Rockledge Dr. MSC [***];Rm [***]
Bethesda, MD 20892-6603 (Fed Ex zip = 20817)
Phone: [***]; Fax: [***]
Email: [***]

The Project Officer is responsible for: (1) monitoring the Contractor's technical progress, including the surveillance and assessment of performance and recommending to the Contracting Officer changes in requirements; (2) interpreting the Statement of Work and any other technical performance requirements; (3) performing technical evaluation as required; (4) performing technical inspections and acceptances required by this contract; and (5) assisting in the resolution of technical problems encountered during performance.

The Contracting Officer is the only person with authority to act as agent of the Government under this contract. Only the Contracting Officer has authority to: (1) direct or negotiate any changes in the Statement of Work; (2) modify or extend the period of performance; (3) change the delivery schedule; (4) authorize reimbursement to the Contractor any costs incurred during the performance of this contract; or (5) otherwise change any terms and conditions of this contract.

The Government may unilaterally change its Project Officer designation.

ARTICLE G.2. KEY PERSONNEL

Pursuant to the Key Personnel clause incorporated in this contract, the following individual is considered to be essential to the work being performed hereunder:

Name	Title
[***], Ph.D	Principal Investigator

ARTICLE G.3. INVOICE SUBMISSION/CONTRACT FINANCING REQUEST AND CONTRACT FINANCIAL REPORT

a. Invoice/Financing Request Instructions and Contract Financial Reporting for NIH CostReimbursement Type Contracts NIH(RC)-4 are attached and made part of this contract. The instructions and the following directions for the submission of invoices/financing

request must be followed to meet the requirements of a "proper" payment request pursuant to FAR 32.9.

These instructions also provide for the submission of financial and personnel reporting required by HHSAR 342.7002.

(1) Invoices/financing requests shall be submitted as follows:

(a) To be considered a "proper" invoice in accordance with FAR 32.9, each invoice shall clearly identify the two contract numbers that appear on the face page of the contract as follows:

Contract No. HHSN266200400100C

ADB Contract No. NO 1-AI-40100

(b) An original and two copies to the following designated billing office:

Contracting Officer
Contract Management Program
National Institute of Allergies and Infectious Diseases, , NIH 6700-B ROCKLEDGE DRIVE
ROOM [***], MSC [***]
BETHESDA MD 20892-7612

(2) Inquiries regarding payment of invoices should be directed to the designated billing office, [***].

ARTICLE G.4. INDIRECT COST RATES

In accordance with Federal Acquisition Regulation (FAR) (48 CFR Chapter 1) Clause 52.216-7 (d)(2), Allowable Cost and Payment incorporated by reference in this contract in Part II, Section I, the cognizant Contracting Officer representative responsible for negotiating provisional and/or final indirect cost rates is identified as follows:

Director, Division of Financial Advisory Services
Office of Acquisition Management and Policy
National Institutes of Health
6100 Building, Room [***]
6100 EXECUTIVE BLVD MSC-[***]
BETHESDA MD 20892-7540

These rates are hereby incorporated without further action of the Contracting Officer.

ARTICLE G.5. GOVERNMENT PROPERTY

a. In addition to the requirements of the clause, GOVERNMENT PROPERTY, incorporated in SECTION I of this contract, the Contractor shall comply with the provisions of DHHS Publication, **Contractor's Guide for Control of Government Property,** 1990, which is incorporated into this contract by reference. Among other issues, this publication provides a summary of the Contractor's responsibilities regarding purchasing authorizations and inventory and reporting requirements under the contract. A copy of this publication is available upon request to the Contracts Property Administrator.

Requests for information regarding property under this contract should be directed to the following office:

Division of Personal Property Services, NIH
6011 Building, Suite 637
6011 EXECUTIVE BLVE MSC [***]
BETHESDA MD 20852-7670
[***]

b. Notwithstanding the provisions outlined in the DHHS Publication, **Contractor's Guide for Control of Government Property,** 1990 which is incorporated in this contract in paragraph a. above, the contractor shall use the form entitled, "Report of Government Owned, Contractor Held Property" for performing annual inventories required under this contract. This form is included as an attachment in SECTION J of this contract.

c. **Contractor-Acquired Government Property - Schedule I-A**

Pursuant to the clause, GOVERNMENT PROPERTY, incorporated in this contract, the Contractor is hereby authorized to acquire the property listed in the attached Schedule I-A for use in direct performance of the contract.

ARTICLE G.6. POST AWARD EVALUATION OF CONTRACTOR PERFORMANCE

a. Contractor Performance Evaluations

Interim and final evaluations of contractor performance will be prepared on this contract in accordance with FAR 42.15. The final performance evaluation will be prepared at the time of completion of work. In addition to the final evaluation, interim evaluations will be prepared every two years.

Interim and final evaluations will be provided to the Contractor as soon as practicable after completion of the evaluation. The Contractor will be permitted thirty days to review the document and to submit additional information or a rebutting statement. If agreement cannot be reached between the parties, the matter will be referred to an individual one level above the Contracting Officer, whose decision will be final.

Copies of the evaluations, contractor responses, and review comments, if any, will be retained as part of the contract file, and may be used to support future award decisions.

b. Electronic Access to Contractor Performance Evaluations

Contractors that have Internet capability may access evaluations through a secure Web site for review and comment by completing the registration form that can be obtained at the following address:

htt ://ocm.od.nihgov/cdmp/cps contractor.htm

The registration process requires the contractor to identify an individual that will serve as a primary contact and who will be authorized access to the evaluation for review and comment. In addition, the contractor will be required to identify an alternate contact who will be responsible for notifying the cognizant contracting official in the event the primary contact is unavailable to process the evaluation within the required 30-day time frame.

SECTION H - SPECIAL CONTRACT REQUIREMENTS

ARTICLE H.1. REIMBURSEMENT OF COSTS FOR INDEPENDENT RESEARCH AND DEVELOPMENT PROJECTS

The primary purpose of the Public Health Service (PHS) is to support and advance independent research within the scientific community. PHS has established effective, time tested and well recognized procedures for stimulating and supporting this independent **research** by selecting from multitudes of applications those research projects most worthy of support within the constraints of its appropriations. The reimbursement through the indirect cost mechanism of independent research and development costs not incidental to product improvement would circumvent this competitive process.

To ensure that all research and development projects receive similar and equal consideration, all organizations may compete for direct funding of independent research and development projects they consider worthy of support by submitting those projects to the appropriate Public Health Service grant office for review. Since these projects may be submitted for direct funding, the Contractor agrees that no costs for any independent research and development project, including all applicable indirect costs, will be claimed under this contract.

ARTICLE H.2. HUMAN SUBJECTS

It is hereby understood and agreed that research involving human subjects shall not be conducted under this contract, and that no material developed, modified, or delivered by or to the Government under this contract, or any subsequent modification of such material, will be used by the Contractor or made available by the Contractor for use by anyone other than the Government, for experimental or therapeutic use involving humans without the prior written approval of the

Contracting Officer.

ARTICLE H.3. CONTINUED BAN ON FUNDING OF HUMAN EMBRYO RESEARCH

a. Pursuant to Public Law(s) cited in paragraph b. , below, NIH is prohibited from using appropriated funds to support human embryo research. Contract funds may not be used for (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). The term “human embryo or embryos” includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.

Additionally, in accordance with a March 4, 1997 Presidential Memorandum, Federal funds may not be used for cloning of human beings.

b.

Public Law and Section No.	Fiscal Year	Period Covered
P.L. 108-199, Title V-General Provisions, Section 510	2004	10/1/03 - 9/30/04

ARTICLE H.4. NEEDLE EXCHANGE

a. Pursuant to Public Law(s) cited in paragraph b., below, contract funds shall not be used to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.

b.

Public Law and Section No.	Fiscal Year	Period Covered
P.L. 108-199, Title V-General Provisions, Section 505	2004	10/1/03 - 9/30/04

ARTICLE H.5. SALARY RATE LIMITATION LEGISLATION PROVISIONS

a. Pursuant to Public Law(s) cited in paragraph b., below, no NIH Fiscal Year funds may be used to pay the direct salary of an individual through this contract at a rate in excess of applicable amount shown for the fiscal year covered. Direct salary is exclusive of fringe benefits, overhead, and general and administrative expenses (also referred to as “indirect cost” or “facilities and administrative (F&A) costs”). Direct salary has the same meaning as the term “institutional base salary.” An individual’s direct salary (or institutional base salary) is the annual compensation that the contractor pays for an individual’s appointment whether that individual’s time is spent on research, teaching, patient care or other activities. Direct salary (or institutional base salary) excludes any income that an individual may be permitted to earn outside of duties to the contractor. The per year

salary rate limit also applies to individuals proposed under subcontracts. It does not apply to fees paid to consultants. If this is a multiple year contract, it may be subject to unilateral modifications by the Government if an individual's salary rate exceeds any salary rate ceiling established in future HHS appropriation acts.

b.

Public Law No.	Fiscal Year	Dollar Amount of Salary Limitation*
P.L. 108-199 Title II, General Provisions, Section 204	2004	Executive Level I

c. Direct salaries which will be paid with FY-04 funds are limited to the Executive Level I rate which was in effect on the date(s) the expense was incurred.

**For contract expenditures using FY-04 funds, the Executive Level Irate for the period 10/1/03 - 12/31/03 is $171,900. Effective 1/1/04, for contract expenditures using FY-04 funds, the Executive Level I rate is $175,700 and will remain at that level until such time as it is determined to raise the Executive Schedule annual rates. See the web site listed below for Executive Schedule rates of pay.*

LINK to EXECUTIVE LEVEL SALARIES: http://www.opnLzov/oca/PAYRATES/index.htm (Click on "Executive Schedule "for the current Fiscal Year's salary rate or scroll down to the "General Schedule Salary Tables from Previous Years" to locate the Executive Level salary rates from previous years)

ARTICLE H.6. EPA ENERGY STAR REQUIREMENTS

Executive Order 13123, "Greening the Government Through Efficient Energy Management" and FAR 23.203 require that when Federal Agencies acquire energy using products, they select, where life-cycle cost-effective, and available, ENERGY STAR® or other energy efficient products.

Unless the Contracting Officer determines otherwise, all energy-using products acquired under this contract must be either an ENERGY STAR® or other energy efficient product designated by the Department of Energy's Federal Energy Management Program (FEMP).

For more information about ENERGY STAR® see http://www.enerpystar.gov/
For more information about FEMP see http://www.eren.doe.gov/femp/procurement

ARTICLE H.7. PUBLICATION AND PUBLICITY

The contractor shall acknowledge the support of the National Institutes of Health whenever publicizing the work under this contract in any media by including an acknowledgment substantially as follows:

"This project has been funded in whole or in part with Federal funds from the National Institute Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN2662004001000."

ARTICLE H.8. PRESS RELEASES

a. Pursuant to Public Law(s) cited in paragraph b., below, the contractor shall clearly state, when issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) the percentage and dollar amount of the total costs of the project or program that will be financed by nongovernmental sources.

b.

Public Law and Section No.	Fiscal Year	Period Covered
P.L. 108-199, Title V-General Provisions, Section 507	2004	10/1/03 - 9/30/04

ARTICLE H.9. REPORTING MATTERS INVOLVING FRAUD, WASTE AND ABUSE

Anyone who becomes aware of the existence or apparent existence of fraud, waste and abuse in NIH funded programs is encouraged to report such matters to the HHS Inspector General's Office in writing or on the Inspector General's Hotline. The toll free number is **1-800-HHS-TIPS (1800-447-8477).** All telephone calls will be handled confidentially. The e-mail address is **Htips(a0s.dhhs.gov** and the mailing address is:

Office of Inspector General
Department of Health and Human Services
TIPS HOTLINE
P.O. Box 23489
Washington, D.C. 20026

ARTICLE H.10. YEAR 2000 COMPLIANCE

In accordance with FAR 39.106, Information Technology acquired under this contract must be Year 2000 compliant as set forth in the following clause(s):

1. **Service Involving the Use of Information Technology**

YEAR 2000 COMPLIANCE–SERVICE INVOLVING THE USE OF INFORMATION TECHNOLOGY

The Contractor agrees that each item of hardware, software, and firmware used under this

contract shall be able to accurately process date data (including, but not limited to, calculating, comparing and sequencing) from, into and between the twentieth and twentyfirst centuries and the Year 1999 and the Year 2000 and leap year calculations.

2. **Noncommercial Supply Items Warranty**

YEAR 2000 WARRANTY—NONCOMMERCIAL SUPPLY ITEMS

The contractor warrants that each noncommercial item of hardware, software, and firmware delivered or developed under this contract and listed below shall be able to accurately process date data (including, but not limited to, calculating, comparing and sequencing) from, into and between the twentieth and twenty-first centuries and the Year 1999 and the Year 2000 and leap year calculations, when used in accordance with the item documentation provided by the contractor, provided that all listed or unlisted items (e.g., hardware, software and firmware) used in combination with such listed item properly exchange date data with it. If the contract requires that specific listed items must perform as a system in accordance with the foregoing warranty, then that warranty shall apply to those listed items as a system. The duration of this warranty and the remedies available to the Government for breach of this warranty shall be as defined in, and subject to, the terms and limitations of any general warranty provisions of this contract provided that notwithstanding any provision to the contrary in such warranty provision(s), or in the absence of any such warranty provision(s), the remedies available to the Government under this warranty shall include repair or replacement of any listed item whose noncompliance is discovered and made known to the contractor in writing within ninety (90) days after acceptance. Nothing in this warranty shall be construed to limit any rights or remedies the Government may otherwise have under this contract with respect to defects other than Year 2000 performance.

YEAR 2000 COMPLIANT ITEMS

None

3. **Commercial Supply Products Warranty**

YEAR 2000 WARRANTY—COMMERCIAL SUPPLY ITEMS

The contractor warrants that each hardware, software and firmware product delivered under this contract and listed below shall be able to accurately process date data (including, but not limited to, calculating, comparing, and sequencing) from, into, and between the twentieth and twenty-first centuries and the Year 1999 and the Year 2000 and leap year calculations, when used in accordance with the product documentation provided by the contractor, provided that all listed or unlisted products (e.g., hardware, software, firmware) used in combination with such listed product properly exchange date data with it. If the contract requires that specific listed products must perform as a system in accordance with the foregoing warranty, then that warranty shall apply to those

listed products as a system. The duration of this warranty and the remedies available to the Government for breach of this warranty shall be as defined in, and subject to, the terms and limitations of the contractor's standard commercial warranty or warranties contained in this contract, provided that notwithstanding any provision to the contrary in such commercial warranty or warranties, the remedies available to the Government under this warranty shall include repair or replacement of any listed product whose noncompliance is discovered and made known to the contractor in writing within ninety (90) days after acceptance. Nothing in this warranty shall be construed to limit any rights or remedies the Government may otherwise have under this contract with respect to defects other than Year 2000 performance.

YEAR 2000 COMPLIANT ITEMS

None

ARTICLE H.11. ANTI -LOBBYING

a. Pursuant to Public Law(s) cited in paragraph c., below, contract funds shall only be used for normal and recognized executive-legislative relationships. Contract funds shall not be used, for publicity or propaganda purposes; or for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself.

b. Contract funds shall not be used to pay salary or expenses of the contractor or any agent acting for the contractor, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature.

c.

Public Law and Section No.	Fiscal Year	Period Covered
for a., above: P.L. 108-199, Title V- General Provisions, Section 503a for	2004	10/1/03 - 9/30/04
b., above: P.L. 108-199, Title V- General Provisions, Section 503b	2004	10/1/03 - 9/30/04

ARTICLE H.12. SHARING RESEARCH DATA

The contractor's data sharing plan, dated September 29, 2004 is hereby incorporated by reference. The contractor agrees to adhere to its plan and shall request prior approval of the Contracting Officer for any changes in its plan.

The NIH endorses the sharing of final research data to expedite the translation of research results into knowledge, products, and procedures to improve human health. This contract is expected to generate research data that must be shared with the public and other researchers. NIH's data sharing policy may be found at the following Web site:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html

NIH recognizes that data sharing may be complicated or limited, in some cases, by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule (see HHS-published documentation on the Privacy Rule at http://www.hhs.gov/ocrf). The rights and privacy of people who participate in NIH-funded research must be protected at all times; thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects.

ARTICLE H.13. HOTEL AND MOTEL FIRE SAFETY ACT OF 1990 (P.L. 101-391)

Pursuant to Public Law 101-391, no Federal funds may be used to sponsor or fund in whole or in part a meeting, convention, conference or training seminar that is conducted in, or that otherwise uses the rooms, facilities, or services of a place of public accommodation that do not meet the requirements of the fire prevention and control guidelines as described in the Public Law. This restriction applies to public accommodations both foreign and domestic.

Public accommodations that meet the requirements can be accessed at: http://www.usfa.fema.gov/hotel/index.htm

ARTICLE H.14. PROHIBITION ON CONTRACTOR INVOLVEMENT WITH TERRORIST ACTIVITIES

The contractor acknowledges that U.S. Executive Orders and Laws, including but not limited to E.O. 13224 and P.L. 107-56, prohibit transactions with, and the provision of resources and support to, individuals and organizations associated with terrorism. It is the legal responsibility of the contractor to ensure compliance with these Executive Orders and Laws. This clause must be included in all subcontracts issued under this contract.

ARTICLE H.15. NOTIFICATION OF EMPLOYEE RIGHTS CONCERNING PAYMENT OF UNION DUES OR FEES

[Note: *This posting requirement does not apply to: contractors with fewer than 15 employees; contractor establishments or construction work sites where no union has been formally recognized by the prime contractor or certified as the exclusive bargaining representative of the prime contractor's employees; contractor establishments where state law forbids enforcement of unionsecurity clauses ("right-to-work" states); or workperformed outside the United States that does not involve the recruitment or employment of workers within the United States.]*

(1) During the term of this contract, the contractor agrees to post a notice*, of such size and in such form as the Secretary of Labor will prescribe, in conspicuous places in and about its plants and offices, including all places where notices to employees are customarily posted. The information required to be included in the notice can be found at http://www.dol.gov/esa/regs/compliance/olmsBeckPosterWithNLRB.pdf except that the

last two sentences must not be included in notices posted in the plants or offices of carriers subject to the Railway Labor Act, as amended (45 U.S.C. 151-188).

(2) The contractor will comply with all provisions of Executive Order 13201 of February 17, 2001, and related rules, regulations, and orders of the Secretary of Labor.

(3) In the event that the contractor does not comply with any of the requirements set forth in paragraphs (1) or (2) above, this contract may be cancelled, terminated, or suspended in whole or in part, and the contractor may be declared ineligible for further Government contracts in accordance with procedures authorized in or adopted pursuant to Executive Order 13201 of February 17, 2001. Such other sanctions or remedies may be imposed as are provided in Executive Order 13201 of February 17, 2001, or by rule, regulation, or order of the Secretary of Labor, or as are otherwise provided by law.

(4) The contractor will include the provisions of paragraphs (1) through (4) herein in every subcontract or purchase order entered into in connection with this contract unless exempted by rules, regulations, or orders of the Secretary of Labor issued pursuant to section 3 of Executive Order 13201 of February 17, 2001, so that such provisions will be binding upon each subcontractor or vendor. The contractor will take such action with respect to any such subcontract or purchase order as may be directed by the Secretary of Labor as a means of enforcing such provisions, including the imposition of sanctions for noncompliance: However, if the contractor becomes involved in litigation with a subcontractor or vendor, or is threatened with such involvement, as a result of such direction, the contractor may request the United States to enter into such litigation to protect the interests of the United States. The full text of Executive Order 13201 is available at http://www.dol.gov/esa/regs/statutes/olms/eol3201.htm. The final rule published in the Federal Register on March 29, 2004 is available at http://www.dol.gov/esa/regs/fedreg/final/2004006823.htm.

*The required employee notice poster may be obtained from the Division of Interpretations and Standards, Office of Labor-Management Standards, U.S. Department of Labor, 200 Constitution Avenue, NW., Room [***], Washington, DC 20210, or from any field office of the Department's

(5) Office of Labor-Management Standards or Office of Federal Contract Compliance Programs. A copy of the poster may also be downloaded from the Office of Labor-Management Standards Web site at http://www.olms.dol.gov. Additionally, contractors may reproduce and use exact duplicate copies of the Department's official poster. See http://www.dol.gov/esa/regs/compliance/olmsBeckPosterWithNLRB.pdf for an exact duplication of the official notification poster.

ARTICLE H.16. OBTAINING AND DISSEMINATING BIOMEDICAL RESEARCH RESOURCES

Unique research resources arising from NIH-funded research are to be shared with the scientific research community. NIH provides guidance, entitled, "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts," (Federal Register Notice, December 23, 1999 [64 FR 72090]), concerning the appropriate terms for disseminating and acquiring these research resources. This guidance, found at http://ott.od.nih.gov/NewPages/64FR72090.pdf. is intended to help contractors ensure that the conditions they impose and accept on the transfer of research tools will facilitate further biomedical research, consistent with the requirements of the Bayh-Dole Act and NIH funding policy.

Note: For the purposes of this Article, the terms, "research tools, " "research materials, " and "research resources" are used interchangeably and have the same meaning.

PART II - CONTRACT CLAUSES

SECTION I - CONTRACT CLAUSES

ARTICLE 1.1. GENERAL CLAUSES FOR **A COST-REIMBURSEMENT RESEARCH AND DEVELOPMENT CONTRACT - FAR** 52.252-2, CLAUSES **INCORPORATED BY REFERENCE (FEBRUARY** 1998)

This contract incorporates the following clauses by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available. Also, the full text of a clause may be accessed electronically at this address: http://www.arnet.gov/far/.

a. FEDERAL ACQUISITION REGULATION (FAR) (48 CFR CHAPTER 1) CLAUSES:

FAR CLAUSE NO.	DATE	TITLE
52.202-1	Jul 2004	Definitions
52.203-3	Apr 1984	Gratuities (Over $100,000)
52.203-5	Apr 1984	Covenant Against Contingent Fees (Over $100,000)
52.203-6	Jul 1995	Restrictions on Subcontractor Sales to the Government (Over $100,000)
52.203-7	Jul 1995	Anti-Kickback Procedures (Over $100,000)
52.203-8	Jan 1997	Cancellation, Rescission, and Recovery of Funds for Illegal or Improper Activity (Over $100,000)
52.203-10	Jan 1997	Price or Fee Adjustment for Illegal or Improper Activity (Over $100,000)
52.203-12	Jun 2003	Limitation on Payments to Influence Certain Federal Transactions (Over $100,000)
52.204-4	Aug 2000	Printed or Copied Double-Sided on Recycled Paper (Over $100,000)
52.204-7	Oct 2003	Central Contractor Registration
52.209-6	Jul 1995	**Protecting the Government's Interests When Subcontracting** With Contractors Debarred, Suspended, or Proposed for Debarment (Over $25,000)
52.215-2	Jun 1999	Audit and Records - Negotiation (Over $100,000)
52.215-8	Oct 1997	Order of Precedence - Uniform Contract Format
52.215-10	Oct 1997	Price Reduction for Defective Cost or Pricing Data
52.215-12	Oct 1997	Subcontractor Cost or Pricing Data (Over $500,000)
52.215-14	Oct 1997	Integrity of Unit Prices (Over $100,000)
52.215-15	Jan 2004	Pension Adjustments and Asset Reversions
52.215-18	Oct 1997	Reversion or Adjustment of Plans for Post-Retirement Benefits (PRB) other than Pensions

52.215-19	**Oct 1997**	**Notification** of Ownership Changes

52.215-21	Oct 1997	Requirements for Cost or Pricing Data or Information Other Than Cost or Pricing Data - Modifications
52.216-7	Dec 2002	Allowable Cost and Payment
52.216-8	Mar 1997	Fixed Fee
52.219-8	May 2004	Utilization of Small Business Concerns (Over $100,000)
52.219-9	Jan 2002	Small Business Subcontracting Plan (Over $500,000)
52.219-16	Jan 1999	Liquidated Damages - Subcontracting Plan (Over $500,000)
52.222-2	Jul 1990	Payment for Overtime Premium (Over $100,000) (Note: The dollar amount in paragraph (a) of this clause is $0 unless otherwise specified in the contract)
52.222-3	Jun 2003	Convict Labor
52.222-26	Apr 2002	**Equal Opportunity**
52.222-35	Dec 2001	**Equal Opportunity for Special Disabled Veterans, Veterans of the Vietnam** Era, and Other Eligible Veterans
52.222-36	Jun 1998	Affirmative Action for Workers with Disabilities
52.222-37	Dec 2001	Employment Reports on Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans
52.223-6	May 2001	Drug-Free Workplace
52.223-14	Aug 2003	Toxic Chemical Release Reporting (Over $100,000)
52.225-1	Jun 2003	Buy American Act - Supplies
52.225-13	Dec 2003	Restrictions on Certain Foreign Purchases
52.227-1	Jul 1995	**Authorization and Consent, Alternate** I (Apr 1984)
52.227-2	Aug 1996	Notice and Assistance Regarding Patent and Copyright Infringement (Over$100,000)
52.227-11	Jun 1997	Patent Rights - Retention by the Contractor (Short Form) (Note: In) **accordance with FAR** 27.303(a)(2), paragraph (f) is modified to include the requirements in FAR 27.303(a)(2)(i) through (iv). The frequency of reporting in (i) is annual
52.227-14	Jun 1987	Rights in Data - General
52.232-9	Apr 1984	Limitation on Withholding of Payments
52.232-17	Jun 1996	Interest (Over $100,000)
52.232-20	Apr 1984	Limitation of Cost
52.232-23	Jan 1986	Assignment of Claims
52.232-25	Oct 2003	Prompt Payment, Alternate I (Feb 2002)

52.232-33	Oct 2003	Payment by Electronic Funds **Transfer–Central** Contractor Registration
52.233-1	Jul 2002	Disputes
52.233-3	Aug 1996	Protest After Award, Alternate I (Jun 1985)
52.242-1	Apr 1984	Notice of Intent to Disallow Costs
52.242-3	May 2001	Penalties for Unallowable Costs (Over $500,000)
52.242-4	Jan 1997	**Certification of Final Indirect Costs**
52.242-13	Jul 1995	Bankruptcy (Over $100,000)
52.243-2	Aug 1987	Changes - Cost Reimbursement, Alternate V (Apr 1984)
52.244-2	Aug 1998	Subcontracts, Alternate II (Aug 1998) *If written consent to subcontract is required, the identified

		subcontracts are listed in ARTICLE B, Advance **Understandings.**
52.244-5	Dec 1996	Competition in Subcontracting (Over $100,000)
52.245-5	May 2004	Government Property (Cost-Reimbursement, Time and Material, or Labor Hour Contract)
52.246-23	Feb 1997	Limitation of Liability (Over $100,000)
52.249-6	Sep 1996	**Termination (Cost-Reimbursement)**
52.249-14	Apr 1984	Excusable Delays
52.253-1	Jan 1991	Computer Generated Forms

b. DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATION (HHSAR) (48 CFR CHAPTER 3) CLAUSES:

HHSAR CLAUSE NO.	DATE	TITLE
352.202-1	Jan 2001	Definitions - with Alternate paragraph (h) (Jan 2001)
352.216-72	Oct 1990	Additional Cost Principles
352.228-7	Dec 1991	Insurance - Liability to Third Persons
352.232-9	Apr 1984	**Withholding of Contract Payments**
352.233-70	Apr 1984	Litigation and Claims
352.242-71	Apr 1984	Final Decisions on Audit Findings
352.270-5	Apr 1984	Key Personnel
352.270-6	Jul 1991	Publications and Publicity
352.270-7	Jan 2001	Paperwork Reduction Act

[End of GENERAL CLAUSES FOR **A COST-REIMBURSEMENT RESEARCH AND DEVELOPMENT CONTRACT** - **Rev.** 07/2004].

ARTICLE I.2. AUTHORIZED SUBSTITUTIONS OF CLAUSES

ARTICLE I.1. of this SECTION is hereby modified as follows:

FAR Clause 52.204-7, CENTRAL CONTRACTOR REGISTRATION (OCTOBER 2003) is deleted in its entirety.

FAR Clause 52.232-33, PAYMENT BY ELECTRONIC FUNDS TRANSFER—CENTRAL CONTRACTOR REGISTRATION (OCTOBER 2003) is deleted in its entirety and FAR Clause 52.232-34, PAYMENT BY ELECTRONIC FUNDS TRANSFER—OTHER THAN CENTRAL CONTRACTOR REGISTRATION (MAY 1999) is substituted therefore.

FAR Clause 52.232-20, LIMITATION OF COST, is deleted in its entirety and FAR Clause 52.232-22, LIMITATION OF FUNDS (APRIL 1984) is substituted therefore. **Note: When this contract is fully funded, FAR Clause 52.232-22, LIMITATION OF FUNDS will no longer apply and FAR Clause 52.232-20, LIMITATION OF COST will become applicable.**

ARTICLE I.3. ADDITIONAL CONTRACT CLAUSES

This contract incorporates the following clauses by reference, with the same force and effect, as if they were given in full text. Upon request, the contracting officer will make their full text available.
a. FEDERAL ACQUISITION REGULATION (FAR) (48 CFR CHAPTER 1) CLAUSES

(1) FAR 52.215-17, Waiver of Facilities Capital Cost of Money (OCTOBER 1997).

(2) FAR 52.227-14, Rights in Data - General (JUNE 1987).

(3) FAR 52.242-3, Penalties for Unallowable Costs (MAY 2001).

b. DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATION (HHSAR) (48 CHAPTER 3) CLAUSES:

(1) HHSAR 352.223-70, Safety and Health (JANUARY 2001). [This clause is provided in full text in SECTION J - ATTACHMENTS.]

(2) HHSAR 352.270-5, Key Personnel (APRIL 1984).

c. NATIONAL INSTITUTES OF HEALTH (NIH) RESEARCH CONTRACTING (RC) CLAUSES:

The following clauses are attached and made a part of this contract:

(1) NIH (RC)-7, Procurement of Certain Equipment (APRIL 1984) (OMB Bulletin 81-16).

ARTICLE I.4. ADDITIONAL FAR CONTRACT CLAUSES INCLUDED IN FULL TEXT

This contract incorporates the following clauses in full text.

FEDERAL ACQUISITION REGULATION (FAR)(48 CFR CHAPTER 1) CLAUSES:

a. FAR Clause 52.244-6, SUBCONTRACTS FOR COMMERCIAL ITEMS (JULY 2004)

(a) Definitions. As used in this clause-

Commercial item, has the meaning contained in Federal Acquisition Regulation 52.202-1, Definitions.

Subcontract, includes a transfer of commercial items between divisions, subsidiaries, or affiliates of the Contractor or subcontractor at any tier.

(b) To the maximum extent practicable, the Contractor shall incorporate, and require its subcontractors at all tiers to incorporate, commercial items or nondevelopmental items as components of items to be supplied under this contract.

(c) (1) The Contractor shall insert the following clauses in subcontracts for commercial items:

(i) 52.219-8, Utilization of Small Business Concerns (MAY 2004) (15 U.S.C. 637(d)(2) and (3)), in all subcontracts that offer further subcontracting opportunities. If the subcontract (except subcontracts to small business concerns) exceeds $500,000 ($1,000,000 for construction of any public facility), the subcontractor must include 52.219-8 in lower tier subcontracts that offer subcontracting opportunities.

(ii) 52.222-26, Equal Opportunity (APR 2002) (E.O. 11246).

(iii) 52.222-35, Equal Opportunity for Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans (DEC 2001) (38 U.S.C. 4212(a)).

(iv) 52.222-36, Affirmative Action for Workers with Disabilities (JUN 1998) (29 U.S.C. 793).

(v) 52.247-64, Preference for Privately Owned U.S.-Flag Commercial Vessels (APR 2003) (46 U.S.C. Appx 1241 and 10 U.S.C. 2631) (flow down required in accordance with paragraph (d) of FAR clause 52.247-64).

(2) While not required, the Contractor may flow down to subcontracts for commercial items a minimal number of additional clauses necessary to satisfy its contractual obligations.

(d) The Contractor shall include the terms of this clause, including this paragraph (d), in subcontracts awarded under this contract.

PART III

SECTION J - LIST OF ATTACHMENTS

The following documents are attached and incorporated in this contract:

1. Statement of Work, September 10, 2004, 3 pages.

2. Invoice/Financing Request and Contract Financial Reporting Instructions for NIH CostReimbursement Type Contracts, NIH(RC)-4, (11/03), 6 pages.

3. Safety and Health, HHSAR Clause 352.223-70, (1/01), 1 page.

4. Procurement of Certain Equipment, NIH(RC)-7, 4/1/84, 1 page.

5. Report of Government Owned, Contractor Held Property, 1 page.

6. Government Property - Schedule I-A, dated September 10, 2004, 1 page.

7. Data Sharing Plan, September 29, 2004

SECTION K - REPRESENTATIONS AND CERTIFICATIONS

The following documents are incorporated by reference in this contract:

1. Representations and Certifications, dated September 13, 2004

ATTACHMENT 1

STATEMENT OF WORK

ASSAYS FOR DETECTION OF NOVEL OR LATENT/OCCULT ADVENTITIOUSAGENTS IN CELL SUBSTRATES

Independently, and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, materials, equipment, and facilities, not otherwise provided by the Government under the terms of this contract, as needed to perform the work set forth below.

The Contractor shall be responsible for 1) developing one or more assays to identify latent and/or occult adventitious agents present in cell substrates, and 2) if approved by the Project Officer, developing a validation plan and conducting studies to validate the assay(s). Each assay must be tested using two cell substrates. To the extent possible, efforts should focus on applying existing technologies, reagents, techniques, and animal strains to the assay development. Assays that show promise during the first stage of development will be candidates for the second stage of development, validation.

Specifically, the Contractor shall:

I. Develop, characterize and validate assays for the detection of novel or latent/occult adventitious agents in cell substrates. Assays can include *in vitro* assays, *in vivo* animal models, and/or assays that contain both an *in vitro* assay and an *in vivo* animal model component.

1. During the first stage of development, characterize assays that can be used to screen for unidentified latent adventitious agents. Examples of potential assays to be developed include:

   a. Assays to identify cellular genes that are normally inactivated but become specifically activated in the presence of a wide range of infectious agents.
   b. Development of degenerative primers for either microarray or PCR analysis to screen for previously unidentified viruses that are related to known viruses.
   c. Use of chemical stimulants to activate latent viruses in the cell substrate. Stimulation could be coupled with a non-specific detection system, such as PERT or TEM to look for activated viruses.
   d. Using whole cell lysate in *in vitro* assays and in animal models to determine if virus is released from latency or otherwise activated following cell lysis.

2. During the first stage of development, characterize sensitive methods to screen for TSE agents in cell substrates. Examples of potential assays to be developed include:

   a. Screening for TSE infection and ability to propagate TSE in cells exposed to BSE contaminated serum.
   b. Assays to determine if cell substrates are producing the variant form of the PrP protein.

3. Upon completion of the first stage of development, the NIAID Project Officer will determine if the assay will be a candidate for further development and validation. The decision process will consist of two steps. Immediately following completion of the assay development stage, the NIAID Project Officer and Contractor will meet to discuss the data, results, and conclusions from the development studies. If the Project Officer determines that sufficient information is available to warrant further development, the Contractor will be directed to prepare a concept validation plan. The concept validation plan will outline the studies to be performed to meet each of the assay validation criteria in accordance with the most current version of the ICH Q2A and Q2B documents. The Project Officer will then review the validation plan in consultation with the Contractor, the Advisory Committee (see section II below), regulatory agencies, and/or other experts as deemed necessary by the Project Officer, to determine if the assay validation plan is appropriate, and, if validated, whether the assay will provide meaningful, relevant information for regulatory agencies and vaccine manufacturers to better characterize novel cell substrates. The final decision on whether or not the assay will be a candidate for validation will be based on the Project Officer's assessment that 1) the assay can be validated; and 2) if validated, the assay will provide meaningful, relevant information for regulatory agencies and vaccine manufacturers to better characterize novel cell substrates. Following selection of an animal model for validation, the Contractor will plan, prepare and conduct validation of the animal model. This will include:

   a. Develop a detailed validation plan. Validation must be performed in accordance with the most current version of the ICH Q2A and Q2B documents. As indicated in ICH Q2A, validation characteristics should include: Accuracy, Precision, Specificity, Detection Limit, Quantitation Limit, Linearity, and Range. The validation plan will include the following information/sections: Cover page, table of contents, purpose, study objective, responsibilities, definitions, summary of completed studies, study description, sample description, materials and supplies, equipment information, test methods,

Standard Operating Procedures (SOPs), test protocol (Test functions describing each validation parameter, how it will be tested, and the acceptance criteria), data handling and analysis, and report requirements.

b. Conduct validation studies according to validation plan.

c. Perform data analysis at the conclusion of the validation studies.

d. Prepare study report. Report will include the following sections/information: Cover page, table of contents, abstract, methods and materials, results, conclusions, and appendices. The `results' section of the study report will be divided into subsections, with each subsection dedicated to one of the validation parameters (based on the test protocol).

II. PARTICIPATE IN ADVISORY COMMITTEE ACTIVITIES

The NIAID Project Officer will form an Advisory Committee to provide expert advice on certain issues related to the ongoing work performed under this contract. The input and advice provided by the Advisory Committee, in conjunction with input from regulatory agencies and the Contractor, will be used by the Project Officer to aid in making decisions regarding assay development and assay validation. The Project Officer will determine the composition and number of members of the Advisory Committee. Members may be added or removed as necessary to meet the needs of the Government. Two-day Advisory Committee meetings will be held twice each year of the contract in the Bethesda, MD area. The Contractor will participate in these meetings to support the Advisory Committee as requested by the Project Officer. Participation will include presenting and discussing test results, and providing expert opinions on methodologies and assay development and validation. The Contractor will also provide additional support for Advisory Committee activities, including providing read ahead documents prior to a committee meeting; scheduling and making all logistical arrangements for Committee meetings; and support the travel of two (2) nonFederal Committee members.

III. PROVIDE FOR AN ORDERLY TRANSITION TO A SUBSEQUENT CONTRACTOR OR THE GOVERNMENT ON OR BEFORE THE COMPLETION DATE OF THIS CONTRACT

Twelve months prior to the completion date of this contract, a transition plan, which will include access to all data, shall be submitted to the NIAID Project Officer for review and approval, in order to ensure orderly transition of contract-related material to a successor contractor or the Government. The transition plan will include a detailed description of the methods and procedures for the transition, the timeline for preparation and delivery of various materials, and the mechanism(s) to be used to provide access to all data generated under this contract.

ATTACHMENT 2

INVOICE/FINANCING REQUEST AND CONTRACT FINANCIAL REPORTING
INSTRUCTIONS FOR NIH COST-REIMBURSEMENT CONTRACTS, NIH(RC)-4

General: The contractor shall submit claims for reimbursement in the manner and format described herein and as illustrated in the sample invoice/financing request.

Format: Standard Form 1034, "Public Voucher for Purchases and Services Other Than Personal," and Standard Form 1035, "Public Voucher for Purchases and Services Other Than Personal— Continuation Sheet," or reproduced copies of such forms marked ORIGINAL should be used to submit claims for reimbursement. In lieu of SF-1034 and SF1035, claims may be submitted on the payee's letter-head or self-designed form provided that it contains the information shown on the sample invoice/financing request.

Number of Copies: As indicated in the Invoice Submission Clause in the contract.

Frequency: Invoices/financing requests submitted in accordance with the Payment Clause shall be submitted monthly unless otherwise authorized by the contracting officer.

Cost Incurrence Period: Costs incurred must be within the contract performance period or covered by precontract cost provisions.

Billing of Costs Incurred: If billed costs include: (I) costs of a prior billing period, but not previously billed; or (2) costs incurred during the contract period and claimed after the contract period has expired, the amount and month(s) in which such costs were incurred shall be cited.

Contractor's Fiscal Year: Invoices/financing requests shall be prepared in such a manner that costs claimed can be identified with the contractor's fiscal year.

Currency: All NIH contracts are expressed in United States dollars. When payments are made in a currency other than United States dollars, billings on the contract shall be expressed, and payment by the United States Government shall be made, in that other currency at amounts coincident with actual costs incurred. Currency fluctuations may not be a basis of gain or loss to the contractor. Notwithstanding the above, the total of all invoices paid under this contract may not exceed the United States dollars authorized.

Costs Requiring Prior Approval: Costs requiring the contracting officer's approval, which are not set forth in an Advance Understanding in the contract shall be so identified and reference the Contracting Officer's Authorization (COA) Number. In addition, any cost set forth in an Advance Understanding shall be shown as a separate line item on the request.

Invoice/Financing Request Identification: Each invoice/financing request shall be identified as either:

(a) Interim Invoice/Contract Financing Request - These are interim payment requests submitted during the contract performance period.

(b) Completion Invoice - The completion invoice is submitted promptly upon completion of the work; but no later than one year from the contract completion date, or within 120 days after settlement of the final indirect cost rates covering the year in which this contract is physically complete (whichever date is later). The completion invoice should be submitted when all costs have been assigned to the contract and all performance provisions have been completed.

(c) Final Invoice -A final invoice maybe required after the amounts owed have been settled between the Government and the contractor (e.g., resolution of all suspensions and audit exceptions).

Preparation and Itemization of the Invoice/Financing Request: The contractor shall furnish the information set forth in the explanatory notes below. These notes are keyed to the entries on the sample invoice/financing request.

(a) Designated Billing Office Name and Address - Enter the designated billing office and address, identified in the Invoice Submission Clause of the contract, on all copies of the invoice/financing request.

(b) Invoice/Financing Request Number - Insert the appropriate serial number of the invoice/financing request.

(c) Date Invoice/Financing Request Prepared -Insert the date the invoice/financing request is prepared.

(d) Contract Number, ADB Number and Date - Insert both the contract number and the ADB number (which appears in the upper left hand corner of the face page of the contract), and the effective date of the contract.

(e) Payee's Name and Address - Show the contractor's name (as it appears in the contract), correct address, and the title and phone number of the responsible official to whom payment is to be sent. When an approved assignment has been made by the contractor, or a different payee has been designated, then insert the name and address of the payee instead of the contractor.

(f) Total Estimated Cost of Contract - Insert the total estimated cost of the contract, exclusive of fixed-fee. For incrementally funded contracts, enter the amount currently obligated and available for payment.

(g) Total Fixed-Fee - Insert the total fixed-fee (where applicable). For incrementally funded contracts, enter the amount currently obligated and available for payment.

(h) Billing Period - Insert the beginning and ending dates (month, day, and year) of the period in which costs were incurred and for which reimbursement is claimed.

(i) Incurred Cost - Current - Insert the amount billed for the major cost elements, adjustments, and adjusted amounts for the current period.

(j) Incurred Cost - Cumulative - Insert the cumulative amounts billed for the major cost elements and adjusted amounts claimed during this contract.

(k) Direct Costs -Insert the major cost elements. For each element, consider the application of the paragraph entitled "Costs Requiring Prior Approval" on page 1 of these instructions.

(1) Direct Labor - Include salaries and wages paid (or accrued) for direct performance of the contract. For Key Personnel, list each employee on a separate line. List other employees as one amount unless otherwise required by the contract.

(2) Fringe Benefits - List any fringe benefits applicable to direct labor and billed as a direct cost. Fringe benefits included in indirect costs should not be identified here.

(3) Accountable Personal Property - Include permanent research equipment and general purpose equipment having a unit acquisition cost of $1,000 or more and having an expected service life of more than two years, and sensitive property regardless of cost (see the DHHS *Contractor's Guide for Control of Government Property).* Show permanent research equipment separate from general purpose equipment. Prepare and attach the NIH Form entitled, "Report of Government Owned, Contractor Held Property," in accordance with the following instructions:

List each item for which reimbursement is requested. A reference shall be made to the following (as applicable):

The item number for the specific piece of equipment listed in the Property Schedule.

The Contracting Officer's Authorization letter and number, if the equipment is not covered by the Property Schedule.
An asterisk (*) shall preced the item if the equipment is below the approval level.

(4) Materials and Supplies -Include equipment with unit costs of less than $1,000 or an expected service life of two years or less, and consumable material and supplies regardless of amount.

(5) Premium Pay - List remuneration in excess of the basic hourly rate.

(6) Consultant Fee - List fees paid to consultants. Identify consultant by name or category as set forth in the contract's Advance Understanding or in the COA letter, as well as the effort (i.e., number of hours, days, etc.) and rate being billed.

(7) Travel - Include domestic and foreign travel. Foreign travel is travel outside of Canada, the United States and its territories and possessions. However, for an organization located outside Canada, the United States and its territories and possessions, foreign travel means travel outside that country. Foreign travel must be billed separately from domestic travel.

(8) Subcontract Costs - List subcontractor(s) by name and amount billed.

(9) Other- List all other direct costs in total unless exceeding $1,000 in amount. If over $1,000, list cost elements and dollar amounts separately. If the contract contains restrictions on any cost element, that cost element must be listed separately.

(l) Cost of Money (COM) - Cite the COM factor and base in effect during the time the cost was incurred and for which reimbursement is claimed.

(m) Indirect Costs–Overhead -Identify the cost base, indirect cost rate, and amount billed for each indirect cost category.

(n) Fixed-Fee Earned -Cite the formula or method of computation for the fixed-fee (if any). The fixed-fee must be claimed as provided for by the contract.

(o) Total Amounts Claimed -Insert the total amounts claimed for the current and cumulative periods.

(p) Adjustments - Include amounts conceded by the contractor, outstanding suspensions, and/or disapprovals subject to appeal.

(q) Grand Totals

The contracting officer may require the contractor to submit detailed support for costs claimed on one or more interim invoices/financing requests.

FINANCIAL REPORTING INSTRUCTIONS:

These instructions are keyed to the Columns on the sample invoice/financing request.

Column A–Expenditure Category- Enter the expenditure categories required by the contract.

Column B–Cumulative Percentage of Effort/H rs. -Negotiated - Enter the percentage of effort or number of hours agreed to doing contract negotiations for each employee or labor category listed in Column A.

Column C–Cumulative Percentage of Effort/Hrs.-Actual - Enter the percentage of effort or number of hours worked by each employee or labor category listed in Column A.

Column D–Incurred Cost-Current - Enter the costs, which were incurred during the current period.

Column E–Incurred Cost-Cumulative - Enter the cumulative cost to date.

Column F–Cost at Completion - Enter data only when the contractor estimates that a particular expenditure category will vary from the amount negotiated. Realistic estimates are essential.

Column G– Contract Amount - Enter the costs agreed to during contract negotiations for all expenditure categories listed in Column A.

Column H–Variance (Over or Under) - Show the difference between the estimated costs at completion (Column F) and negotiated costs (Column G) when entries have been made in Column F. This column need not be filled in when Column F is blank. When a line item varies by plus or minus 10 percent, i.e., the percentage arrived at by dividing Column F by Column G, an explanation of the variance should be submitted. In the case of an overrun (net negative variance), this submission shall not be deemed as notice under the Limitation of Cost (Funds) Clause of the contract.

Modifications: Any modification in the amount negotiated for an item since the preceding report should be listed in the appropriate cost category.

Expenditures Not Negotiated: An expenditure for an item for which no amount was negotiated (e.g., at the discretion of the contractor in performance of its contract) should be listed in the appropriate cost category and all columns filled in, except for G. Column H will of course show a 100 percent variance and will be explained along with those identified under H above.

SAMPLE INVOICE/FINANCING REQUEST AND CONTRACT FINANCIAL REPORT

(a) Billing Office Name and Address NATIONAL INSTITUTES OF HEALTH National Institute of Allergies and Infectious Diseases, CMP 6700B Rockledge Drive Room [***], MSC [***] Bethesda, MD 20892-7612	(b) Invoice/Financing (c) Date Invoice	Request No.	
		Prepared	
		No.	
(e) Payee's Name and Address ABC CORPORATION	(d) Contract ADB No. Effective	Date Cost	

100 Main Street Anywhere, USA zip code		
	(f) Total Estimated	Fee
Attn: Name, Title, & Phone Number of Official to Whom Payment is Sent	(g) Total Fixed	

(h) This invoice/financing request represents reimbursable costs for the period from to

Expenditure Category* A	Cumulative Percentage [ILLEGIBLE] Negotiated B	Actual C	(i) Current D	Incurred Cost (j) Cumulative E	Cost at Completion F	Contract Amount G	Variance H
(k) Direct Costs:							
(1) Direct Labor							
(2) Fringe Benefits							
(3) Accountable Property (attach HHS-565)							
(4) Materials & Supplies							
(5) Premium Pay							
(6) Consultant Fees							
(7) Travel							
(8) Subcontracts							
(9) Other							
Total Direct Costs							
(l) Cost of Money							
(m) Overhead							
G&A							
(n) Fixed Fee							
(o) Total Amount Claimed							
(p) Adjustments							
(q) Grand Totals							

I certify that all payments are for appropriate purposes and in accordance with the contract.

(Name of Official) Attach details as specified in the contract	(Title)	

ATTACHMENT 3

HHSAR 352.223-70 SAFETY AND HEALTH (JANUARY 2001)

(a) To help ensure the protection of the life and health of all persons, and to help prevent damage to property, the Contractor shall comply with all Federal, State and local laws and regulations applicable to the work being performed under this contract. These laws are implemented and/or enforced by the Environmental Protection Agency, Occupational Safety and Health Administration and other agencies at the Federal, State and local levels (Federal, State and local regulatory/enforcement agencies).

(b) Further, the Contractor shall take or cause to be taken additional safety measures as the Contracting Officer in conjunction with the project or other appropriate officer, determines to be reasonably necessary. If compliance with these additional safety measures results in an increase or decrease in the cost or time required for performance of any part of work under this contract, an equitable adjustment will be made in accordance with the applicable "Changes" Clause set forth in this contract.

(c) The Contractor shall maintain an accurate record of, and promptly report to the Contracting Officer, all accidents or incidents resulting in the exposure of persons to toxic substances, hazardous materials or hazardous operations; the injury or death of any person; and/or damage to property incidental to work performed under the contract and all violations for which the Contractor has been cited by any Federal, State or local regulatory/enforcement agency. The report shall include a copy of the notice of violation and the findings of any inquiry or inspection, and an analysis addressing the impact these violations may have on the work remaining to be performed. The report shall also state the required action(s), if any, to be taken to correct any violation(s) noted by the Federal, State or local regulatory/enforcement agency and the time frame allowed by the agency to accomplish the necessary corrective action.

(d) If the Contractor fails or refuses to comply promptly with the Federal, State or local regulatory/enforcement agency's directive(s) regarding any violation(s) and prescribed corrective action(s), the Contracting Officer may issue an order stopping all or part of the work until satisfactory corrective action (as approved by the Federal, State or local regulatory/enforcement agencies) has been taken and documented to the Contracting Officer. No part of the time lost due to any stop work order shall be subject to a claim for extension of time or costs or damages by the Contractor.

(e) The Contractor shall insert the substance of this clause in each subcontract involving toxic substances, hazardous materials, or operations. Compliance with the provisions of this clause by subcontractors will be the responsibility of the Contractor.

(End of clause)

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ATTACHMENT 4

PROCUREMENT OF CERTAIN EQUIPMENT

Notwithstanding any other clause in this contract, the Contractor will not be reimbursed for the purchase, lease, or rental of any item of equipment listed in the following Federal Supply Groups, regardless of the dollar value, without the prior written approval of the Contracting Officer.

67 - Photographic Equipment
69 - Training Aids and Devices
70 - General Purpose ADP Equipment, Software, Supplies and Support (Excluding 7045ADP Supplies and Support Equipment.)
71 - Furniture
72 - Household and Commercial Furnishings and Appliances
74 - Office Machines and Visible Record Equipment
77 - Recreational and Athletic Equipment
78 - Musical Instruments, Phonographs, and Home-type Radios

When equipment in these Federal Supply Groups is requested by the Contractor and determined essential by the Contracting Officer, the Government will endeavor to fulfill the requirement with equipment available from its excess personal property sources, provided the request is made under a contract. Extensions or renewals of approved existing leases or rentals for equipment in these Federal Supply Groups are excluded from the provisions of this article.

ATTACHMENT 5 GOVERNMENT

PROPERTY - SCHEDULE

CONTRACTOR: **REPORT OF GOVERNMENT CONTRACTOR HELD** **CONTRACT NUMBER** **OWNED, PROPERTY**

ADDRESS

REPORT DATE:

CLASSIFICATION **FISCAL YEAR:**

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PROPERLY UNDER A-IFR--5'25K

SIGNED BY: DATE SIGNED:

ATTACHMENT 6

GOVERNMENT PROPERTY - SCHEDULE

CONTRACTOR-ACQUIRED GOVERNMENT PROPERTY - SCHEDULE I-A

Quantity	Equipment	Cost/item*	Total cost
1	[***]	[***]	[***]
1	[***]	[***]	[***]
3	[***]	[***]	[***]
3	[***]	[***]	[***]
1	[***]	[***]	[***]
	TOTAL		[***]

*+/- [***] variance related to cost allowed for each line item without prior approval of the Contracting Officer.

ATTACHMENT 7

DATA SHARING PLAN

Date: September 29, 2004

The contractor (Isis Pharmaceuticals, Inc.) shall present at appropriate scientific meetings and submit for publication significant data arising as a direct result of performing under the contract. The contractor, in discussions with the project officer, will identify suitable journals for publication, with a bias toward open access journals, and appropriate technical and commercial conferences for presentations. The contractor may seek patent protection of any inventions conceived or reduced to practice as a result of its performing under the contract. The contractor will retain title and exclusive rights to commercialize such information and inventions and fully intends to make such information and inventions commercially available. In addition, the contractor intends to make commercially available the intellectual property underlying its TIGER methodology, as well as primers (including chemical modifications) and protocols not developed as a direct result of performing under the contract.

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: November 5, 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: November 5, 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 September 30, 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: November 5, 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.