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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, 2002

OR

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE 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 incorporations or organization)	(I.R.S. Employer Identification No.)

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

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

(Former name, former address and former fiscal year, if changed since last report)

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.

(1) Yes ☒ No o (2) Yes ☒ No o

Indicate the number of shares outstanding of each of the issuer's classes of common stock, as of the latest practicable date.

Common stock $.001 par value	**55,136,020 shares**
(Class)	(Outstanding at October 31, 2002)

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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

	September 30, 2002	December 31, 2001
	(Unaudited)	(Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 93,079	$ 127,011
Short-term investments	198,944	185,007
Contracts receivable	10,881	10,360
Inventory	13,074	—
Other current assets	3,666	6,438
Total current assets	319,644	328,816
Property, plant and equipment, net	47,211	28,245
Licenses, net	31,369	32,361
Patents, net	19,059	16,735
Deposits and other assets	5,204	6,605
Long-term investments	2,037	4,299
Total assets	$ 424,524	$ 417,061
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 11,382	$ 6,126
Accrued compensation	4,479	5,646
Accrued liabilities	9,269	3,942
Amount due to affiliates	2,924	—
Current portion of deferred revenues	20,379	22,696
Current portion of long-term obligations	10,465	9,837
Total current liabilities	58,898	48,247
Long-term deferred revenue, less current portion	16,220	20,005
Long-term obligations, less current portion	178,840	125,710
Stockholders' equity:		

Series A Convertible Exchangeable 5% Preferred stock, $.001 par value, zero and 120,150 shares authorized, issued and outstanding at September 30, 2002 and December 31, 2001, respectively	—	12,015
Accretion of Series A Preferred stock dividends	—	1,711
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value, 16,620 shares authorized, 12,015 shares issued and outstanding at September 30, 2002 and December 31, 2001	12,015	12,015
Accretion of Series B Preferred stock dividends	1,699	1,222
Common stock, $.001 par value, 100,000,000 shares authorized, 55,011,691 and 53,750,318 shares issued and outstanding at September 30, 2002 and December 31, 2001, respectively	56	54
Additional paid-in capital	600,716	582,258
Deferred compensation	(12)	(245)
Accumulated other comprehensive income (loss)	(12)	660
Accumulated deficit	(443,896)	(386,591)
Total stockholders' equity	170,566	223,099
Total liabilities and stockholders' equity	$ 424,524	$ 417,061

Note: The balance sheet at December 31, 2001 has been derived from the audited financial statements at that date.

See accompanying notes.

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

	Three months ended September 30,		Nine months ended September 30,	
	2002	2001	2002	2001
Revenue:				
Research and development revenue under collaborative agreements	$ 16,977	$ 16,892	$ 49,580	$ 24,795
Research and development revenue from affiliates	3,313	2,360	8,434	6,508
Licensing and royalty revenue	10	52	306	226
Total revenue	20,300	19,304	58,320	31,529
Expenses:				
Research and development	35,470	19,895	93,983	58,954
General and administrative	2,244	2,333	6,915	7,926
Compensation (benefit) related to stock options	95	1,783	(3,011)	3,054
Total operating expenses	37,809	24,011	97,887	69,934
Loss from operations	(17,509)	(4,707)	(39,567)	(38,405)
Equity in loss of affiliates	(3,454)	(5,142)	(13,180)	(13,300)
Investment income	2,207	1,554	6,243	4,637
Interest expense	(3,796)	(4,022)	(12,591)	(11,139)
Loss on prepayment of 14% Notes	—	—	(2,294)	—
Gain on prepayment of 12% Notes	4,976	—	4,976	—
Net loss	(17,576)	(12,317)	(56,413)	(58,207)
Accretion of dividends on preferred stock	(222)	(326)	(892)	(968)
Net loss applicable to common stock	$ (17,798)	$ (12,643)	$ (57,305)	$ (59,175)
Basic and diluted net loss per share	$ (0.33)	$ (0.29)	$ (1.06)	$ (1.43)
Shares used in computing basic and diluted net loss per share	54,708	43,869	54,253	41,517

See accompany notes.

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

	Nine months ended September 30,	
	2002	2001
Net cash (used in) provided by operating activities	$ (84,364)	$ 4,774
Investing activities:		
Short-term investments	(14,609)	(112,354)
Property and equipment	(22,978)	(5,151)
Other assets	(4,114)	(18,637)
Investment in affiliates	(8,949)	(4,851)
Net cash used in investing activities	(50,650)	(140,993)
Financing activities:		
Net proceeds from issuance of equity securities	7,563	101,895
Net proceeds from issuance of convertible debt	120,921	—
Proceeds from long-term borrowings	28,245	9,277
Principal payment on prepayment of debt	(52,705)	—
Principal payments on debt and capital lease obligations	(2,942)	(2,257)
Net cash provided from financing activities	101,082	108,915
Net decrease in cash and cash equivalents	(33,932)	(27,304)
Cash and cash equivalents at beginning of period	127,011	39,615
Cash and cash equivalents at end of period	$ 93,079	$ 12,311
Supplemental disclosures of cash flow information:		
Interest paid	$ 34,578	$ 1,740
Supplemental disclosures of non-cash financing activities:		
Additions to debt for licensing costs	$ 1,400	$ 13,500
Repayment of debt with common stock	$ —	$ 5,000
Conversion of preferred stock into common stock	$ 14,142	$ —

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED FINANCIAL STATEMENTS
September 30, 2002
(Unaudited)

1. Basis of Presentation

The unaudited interim financial statements for the three and nine month periods ended September 30, 2002 and 2001 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 2001. The financial statements include all adjustments (consisting only of normal recurring adjustments) which the Company 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, 2001 included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

Revenue Recognition

Revenue is generally recognized when all contractual obligations have been satisfied and collection of the resulting receivable is reasonably assured.

Research and development revenue under collaborative agreements

Research and development revenue under collaborative agreements is recognized as the related expenses are incurred, up to contractual limits. Payments received under these agreements that relate to future performance are deferred and recorded as revenue earned over their specified future performance period. Revenue that relates to nonrefundable, up-front fees is recognized over the period of the contractual arrangements as performance obligations related to the services to be provided have been satisfied. Revenue that relates to milestones is recognized upon completion of the milestone's performance requirement. Isis recognizes revenue from federal research grants during the period in which the related expenditures are incurred. Revenue from our Vitravene product sales is recognized as the product is shipped. Revenue associated with our clinical product sales is recognized as product is delivered.

As part of the Company's alliance with Eli Lilly and Company, Lilly provided a $100.0 million interest-free loan to fund the research collaboration. As of September 30, 2002, Isis had drawn down $40.0 million on the $100.0 million loan. Isis discounted the $40.0 million that had been drawn on the loan as of

September 30, 2002, 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 is 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 Isis by Lilly to help fund the research collaboration, and Isis is accounting for the difference as deferred revenue related to the collaboration, which is recognized as revenue over the period of performance.

Research and development revenue from affiliates

Research and development revenue from affiliates is recognized as the related expenses are incurred, up to contractual limits. Revenue related to milestones is recognized upon completion of the milestone's performance requirement, unless consideration for achievement of the milestone is in cash in exchange for the Company's common stock.

Licensing and royalty revenue

Licensing and royalty revenue for which no services are required to be performed in the future is recognized immediately, if collectibility is reasonably assured.

Inventory

Inventory is stated at the lower of cost or market. Inventory consists of raw materials, work in process and finished goods.

Use of Estimates

The preparation of 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 financial statements and accompanying notes. Actual results could differ from those estimates.

Accounting Pronouncements

In April 2002 the FASB, issued SFAS No. 145, "Rescission of FASB Statements No. 4, 44, and 64, Amendment of FASB Statement No. 13, and Technical Corrections." FASB No. 4 required all gains or losses from extinguishment of debt to be classified as extraordinary items net of income taxes. SFAS No. 145 requires that gains and losses from extinguishment of debt be evaluated under the provisions of Accounting Principles Board Opinion No. 30, and be classified as ordinary items unless they meet the specific criteria for treatment as an extraordinary item. The Company adopted the provisions of SFAS 145 effective January 1, 2002, and applied them to its prepayment in May 2002 of the Company's 14% Senior Subordinated Notes and in July 2002 of the Company's 12% convertible debt. The prepayment of both of the 14% and 12% debt did not meet the specific criteria prescribed by SFAS No. 145 to be considered an extraordinary item and as such was recorded as a component of net loss. The Company does not anticipate that the adoption of this statement will have a material effect on its financial position or results of operations.

In June 2002 the Financial Accounting Standards Board (FASB), issued Statement of Financial Accounting Standards (SFAS) No. 146, "Accounting for Costs Associated with Exit or Disposal Activities." SFAS No. 146 addresses financial accounting and reporting for costs associated with exit or disposal activities and nullifies Emerging Issues Task Force Issues No. 94-3, "Liability Recognition for Certain Employee Termination Benefits and Other Costs to Exit an Activity (including Certain Costs Incurred in a Restructuring)." SFAS No. 146 is effective for exit or disposal activities initiated after December 31, 2002. Isis does not expect the adoption of SFAS No. 146 to have a material effect on its financial condition or results of operations.

2. Inventory

Inventory includes the following categories, net of reserves (in thousands):

	September 30, 2002	December 31, 2001
Raw materials	$ 9,020	$ —
Work-in-process	948	—
Finished goods	3,106	—
	$ 13,074	$ —

3. Strategic Alliances

Affiliates

In April 1999, Orasense Ltd. (Orasense) was formed to develop technology for the oral formulation of oligonucleotide drugs. In January 2000, a second joint venture, HepaSense Ltd. (HepaSense), was formed to treat patients chronically infected with the Hepatitis C virus. Both affiliates are Bermuda limited companies. Each entity's outstanding common stock is owned 80.1% by Isis and 19.9% by Elan International Services. In November 2002, Isis and Elan agreed to extend the Orasense collaboration through December 2002. Additionally, in November 2002, Isis and Elan terminated the HepaSense collaboration. The original HepaSense collaboration was scheduled to end in July 2002. As part of the termination, Elan's funding obligation ended in June 2002. As a result of the termination of the HepaSense collaboration, Isis has regained rights to its antisense drug for Hepatitis C, ISIS 14803.

Elan and its subsidiaries have retained significant minority investor rights that are considered "participating rights' as defined in EITF 96-16 in each entity. Therefore, Isis does not consolidate the financial statements of Orasense or HepaSense, but instead accounts for the investments in each under the equity method of accounting. For the nine months ended September 30, 2002 and 2001, Isis recognized $8.4 million and $6.5 million, respectively, in revenue for research and

development activities performed for these joint ventures. For the three months ended September 30, 2002, Isis reported $3.3 million in revenue primarily associated with Orasense with approximately $267,000 related to final services for HepaSense recognized in the third quarter of 2002. For the three months ended September 30, 2001, Isis reported $2.4 million in revenue for research and development activities performed for both Orasense and HepaSense. These amounts are included as research and development revenue from affiliates for the respective periods.

In April 2002, Isis achieved a development milestone in its HepaSense Ltd. joint venture with Elan triggering a $3.75 million equity purchase by Elan of Isis common stock at a price of $29.74. Elan also received a warrant to purchase 6,304 shares of Isis common stock at an exercise price of $59.48 per share. The result of this transaction increased the Company's cash balance and was not recorded as revenue.

In July 2002, Isis prepaid $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. The prepayment resulted in a gain of approximately $5 million which was recorded in the third quarter of 2002 as a gain from prepayment of debt.

The results of operations of Orasense for the quarter and nine month periods ended September 30, 2002 and 2001 are as follows (in thousands):

	Three months ended September 30,		Nine months ended September 30,	
	2002	2001	2002	2001
Revenue	$ —	$ —	$ —	$ —
Research and development expense	4,039	3,661	8,350	9,294
Net loss	$ (4,039)	$ (3,661)	$ (8,350)	$ (9,294)

The research and development expense for HepaSense for the three months ended September 30, 2002 was associated with close out expenses incurred in the third quarter. The results of operations of

HepaSense for the quarter and nine month periods ended September 30, 2002 and 2001 are as follows (in thousands):

	Three months ended September 30,		Nine months ended September 30,	
	2002	2001	2002	2001
Revenue	$ —	$ —	$ —	$ —
Research and development expense	271	2,760	8,104	6,976
Net loss	$ (271)	$ (2,760)	$ (8,104)	$ (6,976)

Amgen, Inc.

In August 2002, Isis achieved a research milestone in the Company's drug discovery collaboration with Amgen and received an associated milestone payment. The milestone is related to research progress in a three year antisense drug discovery collaboration initiated in December 2001. The milestone was recorded as research and development revenue under collaborative agreements as the milestone performance requirement was completed.

Hybridon, Inc.

In August 2002, Isis and Hybridon cancelled the remaining reciprocal financial obligations related to their Collaboration and License Agreement entered into in May 2001. Under the original terms, Hybridon owed Isis an additional four million shares of Hybridon common stock, payable immediately. Isis owed Hybridon $4.5 million in cash or stock, due in May 2003. The cancellation of the obligations resulted in a decrease to the license carrying value in the amount of $500,000.

Eli Lilly and Company

In September 2002, Isis agreed to manufacture Affinitac during the product launch period for Lilly. The agreement requires Lilly to provide Isis with a loan of up to $21 million to fund the construction of a new manufacturing suite dedicated to Affinitac. Isis will repay the loan from Affinitac success milestones due from Lilly or other product-related cash flows. The loan is secured with the movable equipment purchased for the manufacturing suite. The facility is under construction on Isis' Carlsbad campus in an existing building and is substantially complete.

4. Comprehensive Loss

SFAS No. 130, Reporting Comprehensive Income, requires the Company to report, in addition to net loss, comprehensive loss and its components. A summary follows:

Statements of Comprehensive Loss

	Three months ended September 30,		Nine months ended September 30,	
	2002	2001	2002	2001
Comprehensive loss:				

Change in unrealized gains (losses)	$ 648	$ 447	$ (672)	$ 890
Net loss applicable to common stock	(17,798)	(12,643)	(57,305)	(59,175)
Comprehensive loss	$ (17,150)	$ (12,196)	$ (57,977)	$ (58,285)

5. Debt Issuance and Debt Prepayment

In May 2002, Isis issued in a private placement $125 million of 5 1/2% convertible subordinated notes due May 2009. The Company received approximately $121 million of proceeds net of offering costs.

In May 2002, Isis prepaid its 14% Senior Subordinated Notes totaling approximately $74 million with proceeds the Company received from the above mentioned debt offering. The transaction resulted in a payment of $40.1 million in principal, $32.6 million in accrued interest, and a $2.3 million loss on prepayment of debt which consisted of unamortized issuance costs, unamortized warrants and prepaid interest.

In July 2002, Isis prepaid $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. The prepayment resulted in a gain of approximately $5 million that was recorded in the third quarter of 2002 as a gain from prepayment of debt.

6. Stockholders' Equity

Conversion of Series A Convertible Exchangeable 5% Preferred Stock

At December 31, 2001, Isis had 120,150 shares authorized, issued and outstanding of Series A Convertible Exchangeable 5% Preferred Stock. The shares had a term of six years and were convertible into Isis' common stock on or after March 31, 2002. These also carry a mandatory pay-in-kind dividend of 5.0% per year on the original issue price per share, compounded semi-annually payable only upon conversion into Isis' common stock or cash.

On August 7, 2002, the holder of our Series A Convertible Preferred Stock exercised its option to convert the Series A shares into Isis common stock. The transaction converted the outstanding 120,150 shares of Series A Convertible Preferred Stock into 656,674 shares of Isis common stock using a conversion price of $21.54 per share. Included in the conversion was approximately $2.1 million in preferred stock dividends, which were accrued in prior periods.

7. Subsequent Events

In November 2002, the Company announced the termination of its GeneTrove database product offering and a resulting reorganization of the GeneTrove division. As a result, the Company will reduce its workforce by approximately 25 people. The restructuring plan also provides for the write-down of certain intellectual property related to the GeneTrove database product. The Company will incur a one-time charge of approximately $1.2 million associated with the restructuring in the fourth quarter of 2002. GeneTrove will continue to market its custom target validation services and intellectual property licenses to pharmaceutical industry partners.

In November 2002, Isis and Elan agreed to extend the Orasense collaboration through December 2002. Additionally, in November 2002, Isis and Elan terminated the HepaSense collaboration. The original HepaSense collaboration was scheduled to end in July 2002. As part of the termination, Elan's funding obligation ended in June 2002. As a result of the termination of the HepaSense collaboration, Isis has regained rights to its antisense drug for Hepatitis C, ISIS 14803.

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

In addition to historical information contained in this Report, this Report contains forward-looking statements regarding our business and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks and uncertainties inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation services, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this 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, 2001, which is on file with the U.S. Securities and Exchange Commission and those identified in the section of Item 2 entitled "Risk Factors" beginning on page 20 of this Report. As a result, you are cautioned not to rely on these forward-looking statements.

Since our inception in 1989, we have worked to advance the science of antisense for the development of a new class of drugs. We can design 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 a broad pipeline of 13 antisense products currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including cancer and inflammatory, viral, metabolic and dermatological diseases, and are being studied in intravenous, subcutaneous, topical cream, enema and oral formulations. We achieved marketing clearance for the world's first antisense drug Vitravene® (fomivirsen) in 1998.

Established in 2000, GeneTrove is our functional genomics division, which commercializes the first step of our antisense drug discovery program. GeneTrove capitalizes on the specificity of antisense, using it as a tool to identify what a gene does, which is called gene functionalization, and whether a specific gene is a good target for drug discovery, which is called target validation. GeneTrove provides valuable functional genomics services to the pharmaceutical and biotechnology industry, potentially enhancing and expediting drug discovery and development decisions, and generating near-term revenue for us in the process.

We have collaborations with nine major pharmaceutical partners for these services, including Abbott Laboratories, Inc., Aventis (formerly Rhone-Poulenc Rorer), Amgen Inc., Celera Genomics Group, Chiron Corporation, Eli Lilly and Company, Johnson & Johnson Pharmaceutical Research & Development, LLC, Merck & Co., Inc. and Pharmacia Corporation. We expect these collaborations to fund the functionalization of approximately 1,400 new genes through the timeframe of these agreements, which conclude within the next two to three years. In August 2001 we supplemented our GeneTrove service business with the introduction of a subscription database product. However, GeneTrove was unsuccessful in generating customers for its database product. As a result, in November 2002, we decided to terminate the GeneTrove database product and reduced our workforce accordingly. GeneTrove will continue to market its custom target validation services and intellectual property licenses to pharmaceutical industry partners, as these components of the GeneTrove business are both financially and strategically valuable to us.

Our Ibis Therapeutics division is taking advantage of the investment we have made in RNA-based drug discovery. The division is using its proprietary technology to create small molecule drugs that bind to structured regions of RNA—areas that are not available to antisense drug discovery. RNA is an optimal target as it is universal, simple in structure and predictable. Historically, the division has focused primarily on the research and development of anti-bacterials, anti-virals and anti-fungals, Ibis

has since expanded its program to include a diagnostic application of its technology. Since its inception, Ibis has received significant financial support from various federal government agencies to use its technology for the development of RNA-based countermeasures to biological warfare. In October 2001, Ibis received a two-year contract with the Defense Advanced Research Projects Agency, or DARPA, to develop a sensor to detect infectious agents used in biological warfare attacks. Additionally, in March 2002, Ibis transitioned its government-sponsored research program to discover novel antibacterial drugs for biological warfare defense to the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID. Ibis received a new three-year contract from USAMRIID to advance Ibis' work in developing therapeutic countermeasures to biological warfare and expects to receive funding of up to $2.4 million under this contract.

Critical Accounting Policies

We prepare our 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 estimates and assumptions affect the reported balances and amounts within our financial statements and supporting notes thereto. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, include the following:

Revenue Recognition

We generally recognize revenue when all contractual obligations have been satisfied and we are reasonably assured of collecting the resulting receivable. We often enter into collaborations where we receive nonrefundable up-front payments for prior or future expenditures. In compliance with current accounting rules, we recognize revenue related to up-front payments 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 obligation when the information is not clearly defined in the agreements we enter into. Should different estimates prevail, revenue recognized could be materially different. Agreements where we have made estimates of our continuing obligations include our collaborations with Lilly, Agouron Pharmaceuticals, Inc., a Pfizer company, Amgen, Antisense Therapeutics Limited, Chiron and Merck. The collaboration with Agouron ended in June 2002.

Revenue related to milestones is recognized upon completion of the milestone's performance requirement. During fiscal 2002, we have earned milestones through our research collaborations with Amgen and Merck. In addition, in April 2002, we achieved a non-revenue development milestone in our HepaSense joint venture with Elan, which triggered a $3.75 million equity purchase by Elan of our common stock.

As part of our Lilly alliance, Lilly provided a $100.0 million interest-free loan to fund the research collaboration. As of September 30, 2002 we had drawn down $40.0 million on the $100.0 million loan. We discounted the $40.0 million that had been drawn on the loan as of September 30, 2002 to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We 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, and is accounted for as deferred revenue related to the collaboration, and is recognized as revenue over the period of performance.

Additionally, licensing and royalty agreements we enter into for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable are recognized

as revenue immediately. Licensing and royalty agreements where we have no future obligations include Eyetech Pharmaceuticals in 2001.

Valuation of Intellectual Property

We evaluate our licenses and patent assets for impairment on a quarterly basis, or whenever indicators of impairment exist. During this process, we review our portfolio of 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 challenges or potential challenges to our existing patents, the likelihood of applications being issued, the scope of our issued patents and our experience. In the event that we determine an impairment exists where we had previously determined that one did not exist, it may result in a material adjustment to our financial statements.

In November 2002, we terminated our GeneTrove database product offering. As a result, we reviewed for impairment the intellectual property related to the database product offering. Our review resulted in a write-down of the intellectual property to reflect no value. The amount of the write-down will be reflected as a restructuring charge in the fourth quarter of 2002.

Valuation of Short-Term Investments

We invest our excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends and interest rates. In determining if and when a decline in market value below amortized cost is other-than-temporary, we, together with our external portfolio managers, evaluate the market conditions, offering prices, trends of earnings, price multiples, and other key measures for our investments in debt instruments. When we deem such a decline in value is other than temporary, we recognize an impairment loss in the period operating results to the extent of the decline. To date, we have not had any material losses related to our cash or short-term investments.

Use of Estimates

In preparing our financial statements to conform with accounting principles generally accepted in the United States, we make estimates and assumptions that affect the amounts reported in our financial statements and accompanying notes. These estimates include useful lives for fixed assets for depreciation calculations, useful lives for intellectual property for amortization calculations, estimated lives for license agreements related to deferred revenue, valuation of inventory, and assumptions for valuing stock options. Actual results could differ from these estimates.

Results of Operations

Revenue

Our total revenue for the quarter and nine months ended September 30, 2002, was $20.3 million and $58.3 million, respectively, compared to $19.3 million and $31.5 million, respectively, for the same periods in 2001. The $26.8 million increase in revenue for the nine months ended September 30, 2002, was primarily related to the licensing of our Phase III non-small cell lung cancer compound, Affinitac (formerly known as LY900003 or ISIS 3521) to Eli Lilly and Company in August 2001 and to the company's success in attracting a variety of new partners and technology licensees.

Under the category of research and development revenue under collaborative agreements, for the quarter and nine months ended September 30, 2002, we earned $17.0 million and $49.6 million,

respectively, compared to $16.9 million and $24.8 million, respectively, for the same periods in 2001. The increase of $24.8 million for the nine months ended September 30, 2002 was a result of several collaborations in place during the nine months ended September 30, 2002 which were in effect for only a part of the same period in 2001 or non-existent for the same period of 2001. Our August 2001 Lilly alliance significantly contributed to the increase in 2002 over 2001. Other sources of revenue present in 2002 but not in 2001 included: our GeneTrove partnerships with Amgen, Celera, Chiron, Merck and Pharmacia which were entered into in late 2001 or in 2002; and our Ibis divisions' October 2001 and March 2002 biological warfare defense research program with DARPA and USAMRIID, respectively. The increase in revenue was partially offset by the June 2002 termination of our Pfizer collaboration and the decrease in earned milestones in 2002 compared to 2001.

Research and development revenue from affiliates consisted of revenue associated with our two joint ventures with Elan, Orasense and HepaSense. In November 2002, we and Elan agreed to extend the Orasense collaboration through December 2002. Additionally, in November 2002, we and Elan terminated the HepaSense collaboration. As part of the termination, Elan's funding obligation ended in June 2002. The original HepaSense collaboration was scheduled to end in July 2002. As a result of the termination of the HepaSense collaboration, we have regained rights to our antisense drug for Hepatitis C, ISIS 14803. For the nine months ended September 30, 2002 and 2001, we recognized $8.4 million and $6.5 million, respectively, in revenue for research and development activities performed for these joint ventures. For the three months ended September 30, 2002, we reported $3.3 million in revenue primarily associated with Orasense with approximately $267,000 related to final services for HepaSense recognized in the third quarter of 2002. For the three months ended September 30, 2001, we reported $2.4 million in revenue for research and development activities performed for both Orasense and HepaSense. The increase of $1.9 million for the nine months ended September 30, 2002 in revenue from affiliates was a result of increased development activities performed for each joint venture in 2002 compared to 2001.

Our revenue from licensing activities and royalties was $306,000 for the nine months ended September 30, 2002, compared with $226,000 for the same period in 2001.

Operating Expenses

Total operating expenses for the quarter and nine months ended September 30, 2002 totaled $37.8 million and $97.9 million, respectively, compared to $24.0 million and $69.9 million, respectively, for the same periods of 2001. The increase for the quarter and nine months ended September 30, 2002 was the result of increased research and development expenses in 2002 over 2001, partially offset by a decrease in general and administrative expenses, and a reversal of compensation expense related to variable stock options due to the decrease in market value of our stock. Furthermore, as a result of the drugs we delivered during the three and nine months ended September 30, 2002, the net effect of capitalizing inventory resulted in additional research and development expenses of $2.0 million and $1.7 million, respectively.

Historically, we had expensed drug manufacturing costs as they were incurred. In 2002, in response to the advancement of our pipeline into later stages of clinical development and as a result of the increasing number of clinical supply agreements where we sell drug that we manufacture to partners, we began capitalizing the related manufacturing costs for our drugs. We expense manufacturing costs when we deliver our drugs to partners and as we use our drugs in our own clinical trials. This may result in period to period differences in operating expenses related to the volume of drug production and the timing of drug shipments. In September 2002, we agreed to manufacture Affinitac during the product launch period for Lilly. The facility is under construction at our Carlsbad, California campus in an existing building and is substantially complete. Under the terms of the agreement, we will continue to manufacture Affinitac for clinical use, and we will also produce product for commercial use for approximately three years, after which Lilly plans to assume responsibility for manufacturing. The

agreement has the potential to generate up to $120 million in revenue for us over the next three years, if the Affinitac new drug application is successfully submitted to the FDA in 2003, the drug is approved based on positive results from our Phase III study and its market penetration is in line with our projections.

Under the terms of the agreement with Lilly, as of September 30, 2002, we have capitalized approximately $1.6 million of our internal labor directly associated with the construction of the Affinitac manufacturing facility.

Our research and development expenses consist of costs for antisense drug discovery, including costs associated with our GeneTrove division, antisense drug development, our Ibis Therapeutics' division and R&D Support costs. For the quarter and nine months ended September 30, 2002, we reported total research and development expenditures of $35.5 million and $94.0 million, respectively, compared to $19.9 million and $59.0 million reported in 2001, respectively. The $35.0 million increase for the first nine months in 2002 over 2001 was due to the Affinitac Phase III clinical trials, the development of the 12 other antisense products in our pipeline, including the expenses related to the Phase III trials of alicaforsen (ISIS 2302) in Crohn's disease, our $100 million, multi-year research collaboration with Lilly, and increased gene functionalization and target validation activities in support of our numerous GeneTrove collaborations and database development.

Antisense drug discovery costs for the quarter and nine month periods ended September 30, 2002 totaled $11.7 million and $31.2 million, respectively, compared to $5.2 million and $14.4 million for the same periods of 2001. The increase was principally a result of increased costs associated with the scale-up of our original research collaboration with Lilly and the June 2002 expansion of our original Lilly research collaboration to discover inhibitors for specific gene targets associated with cancer. Also contributing to the increase were costs related to gene functionalization and target validation activities including those to support our GeneTrove partnerships. On November 6, 2002, we announced the termination of the GeneTrove database product offering and the resulting reorganization of the GeneTrove division. As a result, we reduced our workforce by approximately 25 people. The restructuring plan also provides for the write-down of certain intellectual property. Consequently, we will incur a one-time charge of approximately $1.2 million associated with the restructuring during the fourth quarter of 2002. GeneTrove will continue to market its custom target validation services and intellectual property licenses to pharmaceutical industry partners.

Antisense drug development expenditures for the quarter and nine month periods ended September 30, 2002 totaled $16.0 million and $40.6 million, respectively, compared to $9.1 million and $28.4 million for the same periods of 2001. The increase of $12.2 million for the nine months ended September 30, 2002, is primarily a result of additional expenses related to the expansion and advancement of our pipeline. At September 30, 2002 we had 13 products in development including two products, Affinitac and ISIS 2302, in Phase III clinical trials and six products in Phase II clinical trials compared to six in Phase II and III combined for the same period in 2001.

Expenditures related to Affinitac for the three and nine months ended September 30, 2002 were $7.7 million and $14.2 million, respectively, compared to $3.0 million and $8.7 million, respectively, for the same periods of 2001. The increase of $5.5 million for the nine months ended in September 30, 2002 compared to the same period of 2001 was primarily a result of costs related to our Phase III trial. A significant portion of this drug was originally expected to be delivered during the third quarter of 2002, however this is now expected to be delivered in the fourth quarter of 2002. If we and Lilly determine that the data from Isis' on-going Phase III trial are sufficiently positive to support a single study NDA, Lilly and we plan to file the NDA in 2003. If we and Lilly determine that data from two Phase III studies reflecting positive data are required, Lilly and we plan to file the NDA in the late-2004 to 2005 timeframe, with data from both Isis' Phase III trial and Lilly's Phase III trial. In March 2002, Lilly initiated a second planned Phase III trial, which has the potential to support the filing of a NDA application, if an additional study is required.

Our second drug in Phase III clinical trials, ISIS 2302 for Crohn's disease, had development expenditures totaling $2.0 million and $5.3 million for the three and nine months ended September 30, 2002, respectively, compared to $1.5 million and $3.9 million, respectively, for the same periods of 2001. The increase of $1.4 million for the nine months ended September 30, 2002 over the same period in 2001, is a result of our two Phase III trials initiated in November 2001 and June 2002, in the United States and Europe, respectively.

Ibis expenditures for the three and nine months ended September 30, 2002 totaled $2.1 million and $6.3 million, respectively, compared to $1.8 million and $5.3 million, respectively, for the same periods in 2001. The increase of $1.0 million for the nine months ended September 30, 2002 was primarily a result of expenses related to Ibis' performance obligations under its multi-year government contracts with DARPA, awarded in the fourth quarter 2001, and with USAMRIID awarded in March 2002.

R&D Support costs for the quarter and nine month periods ended September 30, 2002, totaled $5.6 million and $16.0 million, respectively, compared to $3.7 million and $10.9 million, respectively, for 2001. The increase is a direct result of increases in our research and development efforts. We continually work to control R&D Support costs, however these costs will generally fluctuate as direct research and development costs increase or decrease.

General and administrative expenses for the three and nine months ended September 30, 2002 totaled $2.2 million and $6.9 million, respectively, compared to $2.3 million and $7.9 million, respectively, for the same periods of 2001. The decrease in expense was a result of certain costs previously included in general and administrative expenses, which we have determined are more accurately reflective of research and development efforts. Also contributing to the decrease was the effect of capitalizing certain costs directly related to the construction of the new Affinitac manufacturing facility for Lilly and costs directly associated with the manufacturing of inventory.

Compensation expense related to stock options for the nine months ended September 30, 2002 included a reversal of $3.0 million in previously recorded non-cash compensation expense related to stock options accounted for as variable stock options. Variable stock options can result in significant increases and decreases in compensation expense as a result of the variability in our stock price. The majority of these options expire at the end of 2002.

Equity in Loss of Affiliates

Equity in loss of affiliates for the quarter and nine month periods ended September 30, 2002 was $3.5 million and $13.2 million, respectively, compared to $5.1 million and $13.3 million, respectively, for the same periods ended September 30, 2001. In November 2002, we and Elan agreed to extend the Orasense collaboration through December 2002. Additionally, in November 2002, we and Elan terminated the HepaSense collaboration. As part of the termination, Elan's funding obligation ended in June 2002. The original HepaSense collaboration was scheduled to end in July 2002. As a result of the extension of the Orasense collaboration and the termination of the HepaSense collaboration, the majority of the equity in loss of affiliates recorded in the third quarter relates to Orasense. We use the equity method of accounting for our investments in Orasense and HepaSense. As a result, we recognized our portion, 80.1%, of the total loss reported by Orasense and HepaSense under equity in loss of affiliates.

Investment Income

For the quarter and nine month periods ended September 30, 2002, investment income was $2.2 million and $6.2 million, respectively, compared to $1.6 million and $4.6 million, respectively, for the same periods of 2001. Although our average cash and short-term investment balance was significantly higher during 2002 compared to 2001, our investment income was directly affected by the

decline in interest rates as a result of current market conditions. Our investment policy allows for investments in premium grade corporate bonds and government backed securities. The rates of return on these types of investments during 2002 were less than those available in 2001.

Interest Expense

Interest expense for the quarter and nine month periods ended September 30, 2002 was $3.8 million and $12.6 million, respectively, compared to $4.0 million and $11.1 million, respectively, for the same periods in 2001. Interest expense increased by $1.5 million during the nine months ended September 30, 2002 compared to the same period of 2001. This increase for the nine months was primarily a result of:

- interest accrued on our 14% Senior Subordinated Notes, which we prepaid on May 1, 2002,
- interest accrued on our borrowings under the Elan lines of credit for our Orasense and HepaSense joint ventures of which a portion of these notes were prepaid,
- interest accrued on the May 1, 2002 issuance of $125 million of 5 1/2% convertible subordinated notes, and
- the effects of the outstanding cumulative borrowing of $40 million from our $100 million loan made available to us by Lilly.

The prepayment of our 14% Senior Subordinated Notes resulted in a payment of $40.1 million in principal, $32.6 million in accrued interest, and a $2.3 million loss on prepayment of these notes, which consisted of unamortized issuance costs, unamortized warrants and prepaid interest. In addition, in July 2002, we prepaid $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. The prepayment resulted in a gain of approximately $5.0 million that is recorded in the third quarter of 2002 as a gain from prepayment of these notes.

Interest and principal payments were deferred on our 14% Senior Subordinated Notes through May 1, 2002, and on our borrowings under the Elan lines of credit for our Orasense and HepaSense joint ventures during the nine months ended September 30, 2002. The 14% Senior Subordinated Notes and a portion of the Elan lines of credit were prepaid in May 2002 and July 2002, respectively.

Loss on Prepayment of 14% Notes

For the nine month period ended September 30, 2002, we reported a $2.3 million loss on the prepayment of approximately $74.0 million of our 14% Senior Subordinated Notes, which represented amounts related to unamortized issuance costs, unamortized warrants and prepaid interest. The loss was recorded in the second quarter of 2002 as a loss from prepayment of 14% notes.

Gain on Prepayment of 12% Notes

For the quarter and nine month periods ended September 30, 2002, we reported a $5.0 million gain on the prepayment of $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. The gain was recorded in the third quarter of 2002 as a gain from prepayment of 12% notes.

Net Loss Applicable to Common Stock

For the three and nine months ended September 30, 2002, we reported a net loss of $17.6 million and $56.4 million, respectively, compared to $12.3 million and $58.2 million for the corresponding periods of 2001. Our net loss applicable to common stock was $17.8 million and $57.3 million for the three and nine months ended September 30, 2002, respectively, and $12.6 million and $59.2 million for the same periods in 2001. The decrease of $1.9 million for the nine months ended September 30, 2002 compared to the same period in 2001, was primarily a result of the $5.0 million gain on prepayment of

12% Notes and increased investment income, offset by the loss on prepayment of 14% Notes and increased interest expense and an increase in loss from operations.

Liquidity and Capital Resources

We have financed our operations with revenue from contract research and development, revenue from the sale or licensing of our intellectual property, the sale of our equity securities, and the issuance of long-term debt. From our inception through September 30, 2002, we have earned approximately $328.6 million in revenue from contract research and development and the sale and licensing of our intellectual property. From our inception through September 30, 2002, we have raised net proceeds of approximately $586.1 million from the sale of equity securities. We have borrowed approximately $262.4 million net of debt issuance costs, under long-term debt arrangements to finance a portion of our operations.

As of September 30, 2002, we had cash, cash equivalents and short-term investments totaling $292.0 million and working capital of $260.7 million. In comparison, we had cash, cash equivalents and short-term investments of $312.0 million and working capital of $280.6 million as of December 31, 2001. The decrease in our cash, cash equivalents and short-term investments, and working capital was primarily due to day-to-day operating expenses and the prepayment of $74.0 million and $19.7 million of debt in the second and third quarters of 2002, respectively, offset by the net proceeds we received from the issuance in the second quarter of $125.0 million of convertible notes.

As of September 30, 2002, our long-term obligations totaled $178.8 million, versus $125.7 million at December 31, 2001. In May 2002, we increased our long-term obligations by completing a convertible debt offering of $125.0 million of 5 1/2% convertible subordinated notes due May 2009, which raised approximately $121.0 million net of issuance costs. We used $74.0 million of the proceeds from this debt offering to prepay 14% debt, which was outstanding as

of May 1, 2002. The prepayment of debt resulted in a payment of $40.1 million in principal, $32.6 million in accrued interest, and a $2.3 million loss on prepayment of debt which consisted of unamortized issuance costs, unamortized warrants and prepaid interest. The $32.6 million of interest expense related to the prepayment of this debt is included in our statement of cash flows for the nine months ended September 30, 2002 in the line item titled net cash provided by (used in) operating activities. The $40.1 million of principal related to this debt prepayment is included under financing activities in the line item titled principal payment on prepayment of debts.

On July 3, 2002 we prepaid $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. This prepayment resulted in a gain of approximately $5.0 million, which was recorded in the third quarter of 2002 as a gain on prepayment of debt. Of the $19.7 million prepayment, $2.1 million was for accrued interest and is included in our statement of cash flows for the nine months ended September 30, 2002 in the line item titled net cash provided by (used in) operating activities. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our growing business. We will continue to use lease financing as long as the terms remain commercially attractive. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments at September 30, 2002 combined with investment income and committed contractual cash payments from our partners will be sufficient to meet our anticipated requirements for at least the next 36 months.

The following table summarizes our contractual obligations as of September 30, 2002. The table provides a breakdown of when obligations become due.

	Payments Due by Period (in 000s)				
Contractual Obligations	**Total**	**Less than 1 year**	**1 - 3 years**	**4 - 5 years**	**After 5 years**
Debt	$ 181,323	$ 7,096	$ 52,713	$ 350	$ 121,164
Capital Lease Obligations	$ 7,982	$ 3,369	$ 4,613	$ —	$ —
Operating Leases	$ 14,941	$ 2,532	$ 4,497	$ 3,870	$ 4,042

Prospective Information

In November 2002, we announced the termination of the GeneTrove database product offering and the resulting reorganization of the GeneTrove division. As a result, we reduced our workforce by approximately 25 people. The restructuring plan also provides for the write-down of certain intellectual property. Consequently, we will incur a one-time charge of approximately $1.2 million associated with the restructuring during the fourth quarter of 2002. GeneTrove will continue to market its custom target validation services and intellectual property licenses to pharmaceutical industry partners.

In November 2002, we and Elan agreed to extend the Orasense collaboration through December 2002. Additionally, in November 2002, we and Elan terminated the HepaSense collaboration. The original HepaSense collaboration was scheduled to end in July 2002. As part of the termination, Elan's funding obligation ended in June 2002. The original HepaSense collaboration was scheduled to end in July 2002. As a result of the termination of the HepaSense collaboration, we have regained rights to our antisense drug for Hepatitis C, ISIS 14803.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this Report 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.

RISKS RELATED TO OUR BUSINESS

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 such receipt 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 could have a similar negative impact.

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 will be successfully commercialized by us or our partners.

If the results of clinical testing indicate that any of our drugs under development are not suitable for commercial use, or if additional testing is required to demonstrate such 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. Most of our resources are being applied to create safe and

effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drug candidates, including some that remain in our pipeline, that have not resulted in proof of efficacy against targeted indications.

If our products are not accepted by the market, we are not likely to generate significant 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 any of our products in development, if approved for commercialization, will be used by doctors 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. We and our partners may not be successful in commercializing 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 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 are unable to obtain additional partners, progress on our drug development programs could be delayed or stop.

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; and
- successfully commercialize existing and future product candidates.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may be negatively affected. 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. Our most advanced drug candidate, Affinitac, is being developed collaboratively with Lilly, with the development funded by Lilly. Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics, Limited, Elan, Merck and OncoGenex Technologies Inc. Failure by any of these pharmaceutical company partners to continue to fund and/or develop these drug candidates would have a material adverse effect on our business.

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. Such competition may negatively impact the partners' focus on and commitment to our drug candidate and, as a result, could delay or otherwise negatively affect the commercialization of such 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.

If our GeneTrove business is unable to market its products and services as planned, we could lose our investment in this technology.

Our business could suffer if pharmaceutical companies do not use our GeneTrove target validation or gene functionalization services. We have invested in the development of a gene target validation and

gene functionalization service business for validation and functionalization of gene targets for drug discovery. If pharmaceutical companies fail to use these services due to competition or other factors, our GeneTrove business could fail to make the planned contribution to our financial performance.

For example, in November we terminated our GeneTrove database product offering and reorganized our GeneTrove division. Consequently, we will incur a one-time charge of approximately $1.2 million associated with the restructuring during the fourth quarter of 2002.

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

Because drug discovery and development and research services require substantial lead time and money prior to commercialization, our expenses have exceeded our revenues since we were founded in January 1989. As of September 30, 2002, our accumulated losses were approximately $444 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. Our current product revenues are derived solely from sales of Vitravene. 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.

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

Most of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments at September 30, 2002, combined with investment income and committed contractual cash payments will be sufficient to meet our anticipated requirements for at least the next 36 months. If we fail to meet our goals regarding commercialization of our drug products, gene function database product and research services and licensing of our proprietary technologies, we may need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- the profile and launch timing of our drugs;
- continued scientific progress in our research, drug discovery and development programs;
- the size of these programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in the marketing of our gene function and research service products; 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 additional funds are raised 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 be required 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. Pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, have never been manufactured on a large scale, and to our knowledge there is no commercial scale oligonucleotide manufacturer in business today. We have a limited 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 are enforced by the FDA 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.

If we cannot successfully build and operate our Affinitac manufacturing suite, the potential success of Affinitac, our revenues, and our relationship with Lilly could suffer.

Under our Commercial Supply Agreement with Lilly, we are building a manufacturing suite to manufacture Affinitac. We have limited experience in developing these types of facilities and may not be able to successfully build or operate the manufacturing suite. If we fail to do so, we may be unable to commercialize or meet the potential demands for Affinitac. This could harm the success of Affinitac, reduce our revenues and disrupt our relationship with Lilly.

We may encounter difficulties in designing, constructing and initiating our manufacturing facility including:

- Governmental regulation of our manufacturing facility, specifically, FDA approvals required for the commercial manufacture of Affinitac;
- Construction delays, including obtaining necessary governmental approvals and permits;
- Cost overruns;
-

Delays in design, shipment and installation of equipment for our facility; and

- Other unforeseeable factors inherent in the construction process.

In addition, our manufacturing experience to date has been limited to production of pre-clinical and clinical quantities of our product candidates and to limited commercial production of Vitravene. We also rely on third party suppliers for some of the key components of Affinitac. As a result, we cannot be certain that our manufacturing facilities or our ability to sustain ongoing production of Affinitac will be able to meet our or Lilly's expectations.

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. Our competitors may succeed in developing drug candidates that are more effective than any drug candidates that we are developing. These competitive developments could make our products obsolete or non-competitive.

Our GeneTrove division competes with others in the use of antisense technology for gene target validation and gene functionalization, as well as with other technologies useful for target validation and gene functionalization. Our competition may provide services having more value to potential customers or may market their services more effectively to potential customers. In either case, our gene functionalization and target validation businesses may not contribute to our financial performance as planned.

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 are unable to protect our patents or our proprietary rights, others may be able to compete more directly against us.

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

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

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve litigation or proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission. 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 might be forced 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 United States 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, such as when a certain product candidate will enter the clinic, when a clinical trial will be

completed or when an application for marketing approval will be filed. Our estimates are based on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If milestones are not achieved when we expect them to be, investors could be disappointed and the price of our securities would likely decrease.

For example, if we and Lilly determine that the data from Isis' on-going Phase III trial are sufficiently positive to support a single study NDA, Lilly and we plan to file the NDA in 2003. If we and Lilly determine that data from two Phase III studies reflecting positive data are required, Lilly and we plan to file the NDA in the late-2004 to 2005 timeframe, with data from both Isis' Phase III trial and Lilly's Phase III trial.

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 management. 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. Our collaboration with Lilly requires us to add a significant number of skilled scientific personnel. Our inability to add these employees may impact the success of our Lilly collaboration.

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 the convertible notes. During the 12 months preceding September 30, 2002, the market price of our common stock has ranged from $6.10 to $27.15 per share. The market price of our securities can be affected by many factors, 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 $66^{2}/_{3}$% 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, special meetings of our stockholders may be called only by the board of directors, the chairman of the board or the chief executive officer. We also have implemented a stockholders' rights plan, also called a poison pill, which could make it uneconomical for a third party to acquire our Company on a hostile basis. These provisions, as well as Delaware law and other of our agreements, may discourage certain types of transactions in which our stockholders might otherwise

receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of our Company without action by our stockholders.

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

We have granted registration rights in connection with the issuance of our securities to Elan International Services, Ltd., Eli Lilly and Company, and Reliance Insurance Company. In the aggregate, these registration rights cover approximately 4,166,667 shares of our common stock which are currently outstanding and additional shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these registration rights are exercised by the holders, it will bring additional shares of our common stock into the market, which may have an adverse effect on the price of our securities.

If the private placement of our $5^{1}/_{2}$% convertible subordinated notes violated securities laws, purchasers in the private placement would have the right to seek refunds or damages.

On May 1, 2002, we issued and sold $125 million of $5^{1}/_{2}$% convertible subordinated notes due 2009 in a private placement transaction. The initial purchasers of the notes in that offering resold the notes to persons reasonably believed to be qualified institutional buyers (as defined in Rule 144A under the Securities Act) and non-U.S. persons (as defined in Regulation S under the Securities Act). On April 24, 2002, an article appeared in a San Diego newspaper regarding this offering in which one of our officers was interviewed. The newspaper article could form the basis for a claim that we have engaged in an unregistered public offering of the convertible notes in violation of the securities laws. We would dispute any such claim. However, if such a claim were made and it prevailed, the initial purchasers and persons who purchase the convertible notes from the initial purchasers in the private offering would have the right, for a period of one year, to obtain recovery of the consideration paid in connection with their purchase of the convertible notes or, if they have already sold the convertible notes, to recover any losses resulting from their purchase of the convertible notes.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES OF 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

For the period ended September 30, 2002, an evaluation was performed under the supervision and with the participation of our management, including the Chief Executive Officer (CEO) and the Chief Financial Officer (CFO), of the effectiveness of the design and operation of our disclosure controls and procedures. Based on that evaluation, our management, including the CEO and CFO, concluded that our disclosure controls and procedures were effective as of September 30, 2002. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2002.

PART II—OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

On July 9, 2001, we filed suit against Sequitur, Inc. in the United States District Court for the Southern District of California. The suit alleges infringement of United States Patent No. 6,001,653 entitled "Human Type 2 RNase H", which was issued to Isis on December 14, 1999. In response to this suit, Sequitur has filed certain counterclaims. We believe that we have meritorious defenses to all of these counterclaims. On December 12, 2001, we filed a second suit against Sequitur, Inc. in the U.S. District Court for the Southern District of California. The suit alleges infringement of U.S. Patent No. 6,326,199 entitled "Gapped 2' Modified Oligonucleotide", which was issued to us on December 4, 2001. Sequitur has answered but not filed any counterclaims. On June 12, 2002 the first and second suits were consolidated for all purposes including through trial. On May 2, 2002, we filed a third suit against Sequitur, Inc. in the United States District Court for the Southern District of California. The suit alleges infringement of (i) United States patent No. 5,959,097 entitled "Antisense Modulation of MEK2 Expression," which was issued to Isis on September 28, 1999, (ii) United States patent No. 5,958,733 entitled "Antisense Modulation of Akt-1 Expression," which was issued to Isis on September 28, 1999, (iii) United States patent No. 6,043,090 entitled "Antisense Inhibition of Human Akt-2 Expression," which was issued to Isis on September 28, 2000, and (iv) United States patent No. 6,096,543 entitled "Antisense Inhibition of Human MEK1 Expression," which was issued to Isis on August 1, 2000.

On September 13, 2002, all of the foregoing actions were dismissed with prejudice pursuant to the stipulation of the parties and the settlement, release and license grant agreement between them. The order to show cause was deemed moot by the Court.

ITEM 2. CHANGES IN SECURITIES AND USE OF PROCEEDS

On August 7, 2002, the holder of our Series A Convertible Preferred Stock exercised its option to convert the Series A shares into Isis common stock. The transaction converted the outstanding 120,150 shares of Series A Convertible Preferred Stock into 656,674 shares of Isis common stock using a

conversion price of $21.54 per share. Included in the conversion was approximately $2.1 million in preferred stock dividends, which were accrued in prior periods.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

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

Not applicable.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

Exhibit Number		Description of Document
10.1	—	Revised and Restated ISIS 3521 Supply Agreement dated September 30, 2002 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).
10.2	—	Loan Agreement dated September 30, 2002 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).
10.3	—	Amendment No. 1 to Isis Pharmaceuticals, Inc.'s 10b5-1 Trading Plan.
99.1	—	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

b. Reports on Form 8-K

On September 16, 2002, the Registrant filed a report on Form 8-K for the announcement of its settlement of litigation pending against Sequitur, Inc. and the related press release dated September 16, 2002. These documents were filed as exhibits to the report (with certain confidential information deleted).

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 14, 2002
/s/ B. LYNNE PARSHALL B. Lynne Parshall, Esq.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	November 14, 2002

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-14 and 15d-14) for the registrant and have:

   a) designed such disclosure controls and procedures 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 quarterly report is being prepared;

   b) evaluated the effectiveness of the registrant's disclosure controls and procedures as of a date within 90 days prior to the filing date of this quarterly report (the "Evaluation Date"); and

   c) presented in this quarterly report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation, 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 in the design or operation of internal controls which could adversely affect the registrant's ability to record, process, summarize and report financial data and have identified for the registrant's auditors any material weaknesses in internal controls; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal controls; and

6. The registrant's other certifying officers and I have indicated in this quarterly report whether there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weakness.

Dated: November 14, 2002

/s/ STANLEY T. CROOKE

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

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-14 and 15d-14) for the registrant and have:

   a) designed such disclosure controls and procedures 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 quarterly report is being prepared;

   b) evaluated the effectiveness of the registrant's disclosure controls and procedures as of a date within 90 days prior to the filing date of this quarterly report (the "Evaluation Date"); and

   c) presented in this quarterly report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. The registrant's other certifying officers and I have disclosed, based on our most recent evaluation, 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 in the design or operation of internal controls which could adversely affect the registrant's ability to record, process, summarize and report financial data and have identified for the registrant's auditors any material weaknesses in internal controls; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal controls; and

6. The registrant's other certifying officers and I have indicated in this quarterly report whether there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weakness.

Dated: November 14, 2002

/s/ B. LYNNE PARSHALL

B. Lynne Parshall, Esq.
Chief Financial Officer

QuickLinks

Exhibit 10.1

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

REVISED AND RESTATED
ISIS 3521 SUPPLY AGREEMENT

This Revised and Restated ISIS 3521 Supply Agreement ("Agreement") is made and entered into as of September 30, 2002 (the "Effective Date") between Eli Lilly and Company, a corporation organized and existing under the laws of the State of Indiana ("LILLY") and Isis Pharmaceuticals, Inc., a corporation organized and existing under the laws of the State of Delaware ("ISIS").

WITNESSETH

WHEREAS, ISIS and LILLY are parties to the Development and License Agreement relating to the development and commercialization of ISIS 3521 (the "Development and License Agreement"),

WHEREAS, ISIS will manufacture, release and deliver ISIS 3521 API to LILLY for manufacture into Product and will also perform CMC activities and transfer to LILLY, or a third party selected by LILLY, the technology to manufacture ISIS 3521, pursuant to the terms set forth herein; and

WHEREAS, the parties hereto agree that the Agreement will amend, restate and supercede that certain ISIS 3521 Clinical Supply Agreement dated August 29, 2001 (the "Clinical Supply Agreement") to reflect supply by ISIS of commercial as well as clinical quantities of ISIS 3521.

NOW, THEREFORE, in consideration of the covenants herein contained, the parties hereto agree as follows:

ARTICLE 1

DEFINITIONS

Capitalized terms used in this Agreement have the meanings set forth in Exhibit 1 hereto.

ARTICLE 2

MANUFACTURE AND SUPPLY OF API

2.1 Subject to the terms and conditions set forth herein, LILLY will provide ISIS with estimates of LILLY's requirements of API in accordance with the forecasting requirements of Section 3.1 below. ISIS will supply LILLY's requirements of API [***], in accordance with the terms of this Agreement.

2.2 ISIS will provide bulk API to LILLY for use in the Manufacture of Products. LILLY will be responsible for the formulation, filling, finishing, labeling and packaging of the Products, including stability studies; provided, however, that, in accordance with Section 6.2, until the Release Technology Transfer is completed, ISIS will perform Product release.

2.3 The parties acknowledge that as of the Effective Date, a third party manufacturer performs the formulation, filling and finishing of Clinical Product for ISIS. LILLY will use commercially reasonable efforts to promptly establish, itself or through a third party manufacturer, the manufacturing process for formulating, filling, and finishing Product. If requested by LILLY, ISIS will cooperate with LILLY, as appropriate, to enable LILLY to enter into an agreement with the third party manufacturer used by ISIS to perform the formulation, filling and finishing of Product at LILLY's expense.

ARTICLE 3

ORDERS, LIMITATION OF SUPPLY, AND RAW MATERIALS

3.1 Forecasting.

(a) ISIS and LILLY will establish a twenty-four (24) month rolling forecast (the "Rolling Production Forecast") that sets forth a good faith estimate of the quantity of API LILLY expects to receive from ISIS within the following twenty-four (24) month period. This Rolling Production Forecast will be updated on the first business day of each month by LILLY's Designated Representative. The first [***] of the Rolling Production Forecast constitute a firm order ("Firm Order"). Months [***] through twenty-four (24) are estimated quantities to be used for planning purposes only. Not later than ten (10) days after the Effective Date, LILLY's Designated Representative will provide ISIS with the first Rolling Production Forecast, which will begin on the first day of the calendar month following the Effective Date. LILLY acknowledges the most efficient way for ISIS to meet its supply obligations under this Agreement is to keep the volume of API consistent each month and therefore LILLY will make reasonable efforts to minimize the month to month fluctuations in the amount of API requested in a Firm Order and to order in full validated lot amounts.

(b) By the fifteenth (15^{th}) of each month, LILLY will issue a purchase order for any Product included in the most recent Firm Order which is not already the subject of a purchase order. On each purchase order, LILLY will designate the amount of API to be billed at the API Clinical Supply Cost versus the API Commercial Supply Price, pursuant to section 5.1(a).

(c) The quantities set forth in a Firm Order will be binding on both parties, and LILLY will be obligated to purchase from ISIS, and ISIS will be obligated to supply, the specified quantities of API. ISIS will not be required to supply, nor will LILLY be required to purchase, API in a quantity exceeding the Firm Order.

(d) Notwithstanding the foregoing:

(i) ISIS will not be required to Deliver during a Calendar Quarter more than ISIS' Quarterly Capacity for applicable capacity levels as further described in Exhibit 2.

(ii) Prior to the Product receiving Marketing Approval, ISIS will not be required to Deliver more than [***] of the API forecasted for a quarter when that quarter was the [***] or [***] quarter (whichever was lower) of a Rolling Production Forecast. In addition, LILLY's forecast for [***] will be no less than [***] kilograms per month.

(iii) After the Product has received Marketing Approval, ISIS will not be required to Deliver more than [***], and LILLY will order no less than [***], of the API forecasted for that quarter when that quarter was the [***] quarter of a Rolling Production Forecast.

(e) ISIS agrees to use commercially reasonable efforts to supply LILLY, upon request, with quantities in excess of the quantity restrictions described in this Section 3.1.

(f) Notwithstanding the foregoing, if [***] then LILLY may cancel the portion of a Firm Order that has not yet been Manufactured; *provided, that* LILLY pays ISIS for certain costs related to the Manufacture of API including [***] Upon a cancellation, as described above, ISIS will credit to LILLY any prepayment made under Section 5.1(a) below against any amount LILLY owes ISIS, including the fees and costs described above against the balance of the prepayment. In this event, the parties acknowledge that ISIS may decrease its capacity level (as described in Exhibit 2) to 0, and that, should ISIS resume production at a later date, LILLY may then owe a new prepayment similar to that described in Section 5.1(a), to be agreed upon between the parties.

(g) ISIS' quarterly capacity for the Manufacture of API for Calendar Years 2003 through 2012 (the "Quarterly Capacity"), indicating the maximum amount of API that LILLY may order from ISIS during each such Calendar Quarter, is set forth in Exhibit 2.

3.2 Limitations of Supply.

(a) In the event that at any time ISIS anticipates that it will be unable to supply in whole or in part the quantities of API set forth in an agreed-upon Firm Order for any reason, including without limitation force majeure, ISIS will notify LILLY in writing as soon as possible of such anticipated shortfall. ISIS will also notify LILLY of the underlying reason for the shortfall, proposed remedial measures, the date such inability to supply the full order of API is expected to end, and a proposed amount of API to be Delivered to LILLY.

(b) If ISIS cannot Manufacture as set forth in this Agreement, ISIS shall so inform LILLY immediately upon the prediction or occurrence of such non-supply. In such event, LILLY shall have the right to Manufacture, or have Manufactured by a contract manufacturer of LILLY's choice, API for LILLY's needs and ISIS shall provide all assistance and relevant information, know-how and data necessary for LILLY in establishing and beginning the Manufacture of API.

(c) ISIS hereby waives any claim it may have, and releases LILLY from any obligation it may have, under Section 2.5(d) of the Development and License Agreement (or any similar provisions of that Agreement) with regard to the Manufacture (as defined in the Development and License Agreement) of the Product in the event of any delay, disability or other problem (regardless of the cause) in ISIS' Manufacture of the Product.

3.3 Raw Materials

ISIS will purchase the Raw Materials used in the Manufacture of API. ISIS will lead the audits of the Raw Material vendors for cGMP compliance. ISIS will not enter into any agreement for the purchase of Raw Materials which will result in any financial obligation of LILLY for [***], or which is inconsistent with the current Rolling Production Forecast, without prior consultation with the MWG.

ARTICLE 4

QUALITY STANDARDS; MANUFACTURING WORKING GROUP

4.1 Quality Standards.

(a) With respect to API in process prior to the time the Quality Agreement is adopted, ISIS will Manufacture such API in accordance with cGMP and the same specifications as applied to the Manufacture of API for use in Clinical Product used in the JVAA Study. Subject to the preceding sentence, ISIS will Manufacture API for use in Product in accordance with the API Specifications, cGMP, the MRD (as applicable), the Quality Agreement and other applicable rules and regulations of all Regulatory Authorities and other regulatory agencies with jurisdiction over the manufacture, use or sale of the API, as then in effect. If cGMP for the U.S. and its foreign equivalent differ, LILLY and ISIS agree that the more stringent requirements will apply. In the event that these requirements conflict, the MWG will discuss the issue and determine how to proceed. ISIS will be responsible for Manufacturing issues related to API safety and regulatory compliance. Each party will promptly notify the other party of any relevant new instructions or specifications required by a Regulatory Authority, and of other applicable rules and regulations of which that party becomes aware. The parties will confer with each other with respect to the best means to comply with such requirement and will allocate any costs of implementing such changes on an equitable basis. In the event that, in LILLY's reasonable judgment, ISIS is unable to timely or completely address any such requirement, LILLY may elect to lead the compliance effort in consultation with the MWG.

(b) ISIS will perform quality control testing, as is specified (i) in the Quality Agreement and API Specifications; and (ii) as required by a Regulatory Authority and by the mutual written consent of the parties, on each lot of API, prior to shipment.

4.2 Certificate of Analysis.

(a) ISIS will provide a Certificate of Analysis to LILLY or its designated agent with each lot of API supplied hereunder. Such Certificate of Analysis will contain the results of the analysis of API as required in the API Specifications, and will certify with respect to each shipment and lot (identified by lot number): (i) the quantity of the shipment, and (ii) that the API delivered was Manufactured and packaged in accordance with the API Specifications and in conformance with cGMP. The Certificate of Analysis will also contain (y) any information in addition to that required pursuant to this subsection (a) as may be required by the Regulatory Authority of the country of destination of API or Product and (z) will certify with respect to each shipment and lot (identified by lot number) that the API delivered was Manufactured and packaged in accordance with any applicable registration commitments filed with any Regulatory Authority; provided, that with respect to clauses (y) and (z) above, LILLY provides to ISIS sufficient documentation and information necessary or useful to enable ISIS to conform with such requirements and commitments. ISIS will provide the results of such analysis to LILLY, along with any supporting data.

(b) LILLY will be under no obligation to accept any Delivered lot of API without an accompanying Certificate of Analysis that conforms to subsection (a) above. ISIS will also make available for LILLY's review ISIS' Manufacturing records for the API, including its master and production batch records, for the purposes of assuring product quality and compliance with agreed-upon Manufacturing procedures as per the following Section 9.3, Quality Assurance Audits.

4.3 Manufacturing Working Group

The MWG consists of 3 members from LILLY and 3 members from ISIS. The members must be individuals who are capable of responding to the technical, financial, quality, and other issues that could arise under this Agreement. The MWG can consult with, and receive assistance from, LILLY and ISIS employees who are not MWG members. The additional objectives of the MWG are (i) with the parties' quality units, to adopt the initial Quality Agreement and MRD and subsequent amendments (if any) to each; (ii) to agree on specific Delivery dates for each Firm Order and discuss and agree upon any current forecasting issues; (iii) monitor the parties' performance under this Agreement, including reviewing, on a periodic basis, forecast accuracy, on-time delivery and API Supply Price elements; and (vi) monitor and review the parties' performance under the Loan Agreement, including disbursements and the use of the loan proceeds. The MWG shall report to the parties at least once each calendar quarter and more frequently as requested. LILLY will designate one of its representatives as chairman of the MWG. In the event of a tied vote, the MWG chairman will refer the matter to the LILLY Product Team Leader, who will have final decision-making authority; however, ISIS will not be required to make any financial investment pursuant to such a decision without its agreement, unless such investment is required under the terms of this Agreement. In the event ISIS disagrees with a decision made by the LILLY Product Team Leader, the issue can be brought to the Oversight Committee (see Section 15.6).

4.4 Quality Agreement.

(a) Promptly after the Effective Date, the MWG will begin developing the initial Quality Agreement for API (the "Quality Agreement"). The Quality Agreement shall be adopted (with appropriate signatures) by November 1, 2002.

(b) The MWG will, at least annually, review the Quality Agreement and will amend it from time to time as necessary through the issuance of a revised section incorporating the modification and stating the effective date of the modification, signed by a duly authorized representative from each

party who is a member of the quality control/quality assurance group, as evidenced by a signed, revised Quality Agreement incorporating the revision number that sets forth the effective date of the modifications and reason for the revision.

(c) The Quality Agreement will describe the parties' quality control, quality assurance and regulatory responsibilities relating to the Manufacture and release of the API by ISIS. The Quality Agreement will include as an exhibit the current standard operating procedures of ISIS, as may be amended by ISIS from time to time, listed in Exhibit 3. ISIS will promptly provide to LILLY an updated set of such standard operating procedures upon LILLY's request. All standard operating procedures used by ISIS in connection with the Manufacture of API will comply with cGMP.

(d) In the event of an inconsistency between the Quality Agreement and the terms of this Agreement, the terms of this Agreement will apply.

4.5 Manufacturing Responsibilities Document.

(a) Promptly after the Effective Date, and in any event no later than the initial commercial or demonstration lot of the Commercial Product, the MWG will adopt a Manufacturing Responsibilities Document ("MRD") addressing the Manufacture and validation of Product.

(b) The MWG will, at least annually, review the MRD and will amend it from time to time through the issuance of a revised section incorporating the modification and stating the effective date of the modification, signed by a duly authorized representative of each party.

(c) In the event of an inconsistency between the MRD and the terms of this Agreement, the terms of this Agreement will apply.

4.6 Procedures Regarding Changes to Manufacturing Process.

(a) Subject to the following, the MWG will consider and agree upon the guidelines and the approval process to be applied to any material change in Manufacturing materials, equipment, processes, procedures, or to the API Specifications proposed by ISIS or LILLY.

(b) During the term of this Agreement, if ISIS or LILLY proposes to make a material change in Manufacturing materials, equipment, processes, procedures, or to the API Specifications, the party proposing the change will notify the MWG and provide information to the MWG regarding such change at a level sufficient to allow the MWG members to evaluate the impact of such change on the Manufacturing Process, and to form a basis for the MWG to determine whether or not to approve such material change.

(c) If there are any additional questions regarding notification and approval that arise during the term of this Agreement, ISIS will submit the questions to the MWG or, if an immediate response is required, will contact LILLY's Quality Assurance function to determine the level of review/notification that may be required by the proposed change. The parties will obtain the prior Regulatory Approval and any other required approvals, if such approval is required, before any such material change is implemented.

4.7 Compliance with Laws.

In performing its obligations under this Agreement, ISIS will comply with all applicable present and future orders, rules, regulations, requirements and laws ("Legal Requirements") of any and all U.S. authorities and agencies, including without limitation laws and regulations applicable to the transportation, storage, use, handling and disposal of hazardous materials (the "U.S. Legal Requirements"), and any Legal Requirements of other countries ("Foreign Legal Requirements") of which it is informed in writing by LILLY. If the U.S. Legal Requirements conflict with the Foreign Legal Requirements, the parties will discuss and agree on how to resolve such conflict.

4.8 Documentation and Record Keeping.

ISIS will keep complete, accurate and authentic accounts, notes, data and records of all of ISIS' work performed under this Agreement, including, but not limited to, complete and adequate records pertaining to the methods and facilities used for the Manufacture in accordance with master production records, batch production records, product history documents (e.g., master formulae, validation packages, specifications, CT batch history documents, batch specific deviation reports, COAs), Standard Operating Procedures ("SOPs"), as well as the applicable regulations so that API may be used in the production of a substance to be used in humans. ISIS will maintain these records for 2 years after expiration of the Products that incorporate the particular API. LILLY will notify ISIS in writing of the expiration of Products that incorporate specific API pursuant to the procedures described in the MRD, and if LILLY changes the expiration date on any Product. SOPs will be maintained for 5 years after the document is superseded or deleted. Upon expiration of the retaining periods for the respective records as provided in this Section and in case ISIS wishes to cease retention of such records, ISIS will notify LILLY so that LILLY may, at its cost, retain such records.

4.9 Reviews.

ISIS will generate and provide annual summary reviews for API Manufacturing and control as well as supporting documents or other information for annual product reviews as agreed by the parties.

ARTICLE 5

SUPPLY PRICE; PAYMENT AND TERMS OF SALE

5.1 Supply Price.

(a) The API Clinical Supply Price will apply to all API supplied to LILLY for use in the Manufacture of Clinical Product which is used prior to receiving Marketing Approval. In addition, the API Clinical Supply Price will apply to API supplied to LILLY for use in the Manufacture of Product which is used in clinical trials after the Product has received Marketing Approval, only where the product used in the clinical trial is provided by LILLY at no cost and is not reimbursable. This pricing concession applies up to a maximum of [***] of the API Delivered by ISIS during the first twenty-four (24) months following receipt of Marketing Approval, [***] of the API Delivered by ISIS during the next twelve (12) months, and [***] of the API Delivered by ISIS during the next twelve (12) months and any Calendar Year thereafter. Should the amount of product needed for such clinical studies exceed the percentage described above, the parties will discuss, in good faith, raising the percentage limitation. In the event that LILLY believes that additional un-reimbursed studies are necessary or advisable, ISIS and LILLY shall discuss the supply price for such Product in good faith. Except as stated above, the API Commercial Supply Price will apply to all API supplied to LILLY. Pursuant to Section 2.03 of the Loan Agreement, LILLY may offset [***] of the API Supply Cost of all product purchased by LILLY hereunder against the outstanding principal and interest due under the Loan Agreement, if any.

LILLY will [***] within twenty (20) days of approval by ISIS of the Raw Materials needed for the demonstration and Validation lots of Product described in the Rolling Production Forecast. In the event of an increase in capacity level (see Exhibit 2), LILLY will prepay ISIS an additional amount such that the aggregate outstanding prepayment from LILLY to ISIS (including all uncredited prepayments already received by ISIS) will equal the prepayment amount specified on Exhibit 2 that is applicable to the new capacity level. Such additional prepayment will be due within twenty (20) days after placing the Firm Order that raises the capacity level. In the event of a decrease in capacity level (see Exhibit 2), ISIS will credit LILLY an amount such that the aggregate outstanding prepayment from LILLY to ISIS (including all uncredited prepayments already received by ISIS) is reduced to the prepayment amount specified on Exhibit 2 that is applicable to the new capacity level. LILLY may apply such credit to any

invoice received by LILLY **more than** thirty (30) days after the Firm Order that decreases the capacity level. ISIS will invoice LILLY for the API Clinical Supply Price and/or the API Commercial Supply Price, as appropriate, of each shipment of API Delivered to LILLY. LILLY will pay each invoice within [***] after receipt of the applicable invoice, subject to the provisions of Section 5.3; *provided, however*, that LILLY may apply any prepayment described above against the invoice for the final two months of the final Firm Order delivered to LILLY, and to the final obligations of LILLY under Section 5.5 of this Agreement. ISIS will promptly refund any portion of this prepayment not credited against LILLY obligations under this Agreement upon termination or expiration of this Agreement. Interest will be charged on late payments consistent with the provisions of subsection (d) below.

(b) LILLY will keep accurate records in sufficient detail to enable ISIS to reconcile LILLY's actual use of API (i.e. for Clinical Product versus Commercial Product) against the use set forth in the applicable purchase order. LILLY will provide these records to ISIS on a quarterly basis. In the event that API purchased at the API Clinical Supply Price is used for Commercial Product, LILLY will pay the difference between the API Clinical Supply Price and the API Commercial Supply Price to ISIS in cash upon receipt of an invoice from ISIS. In the event that API purchased prior to the Marketing Approval for the Commercial Product at the API Commercial Supply Price is used for Clinical Product, ISIS will credit the difference between the API Commercial Supply Price and the API Clinical Supply Price to LILLY on the next invoice provided to LILLY more than thirty (30) days after ISIS has received written notice of the discrepancy.

(c) All payments due hereunder will be paid by wire transfer in U.S. Dollars to such bank account as is designated in writing by ISIS from time to time. LILLY will pay a late payment service charge of [***] per month (or the highest amount allowed by law, if lower than [***] on all past due amounts.

5.2 Delivery.

(a) ISIS will deliver API to a carrier designated by LILLY FCA ISIS' Facility (Incoterms 2000). The shipping and packaging specifications will be agreed upon by the parties.

(b) In the event of a physical loss of work in process or API ordered at the API Clinical Supply price prior to the transfer of title pursuant to the Delivery of API as provided in subsection (a) above, any uninsured portion of the loss will be shared by LILLY and ISIS as follows: [***]. Any deductible will be applied ratably against all items damaged or lost. In the event of a physical loss of work in process or API ordered at the API Commercial Supply Price prior to the transfer of title pursuant to the Delivery of API as provided in subsection (a) above and such loss is not the result of an Uncontrollable Event, any uninsured portion of each loss will be shared by LILLY and ISIS as described above [***] Thereafter, ISIS will absorb any loss related to the remaining affected lots in such loss, and will reimburse LILLY for the cost of any LILLY Raw Materials consumed.

(c) ISIS will use commercially reasonable efforts to Deliver the API to LILLY, or a third party designated by LILLY, on the mutually agreed-upon Delivery date (as determined by the MWG). ISIS will be considered late on a Delivery, if such Delivery has not occurred on the applicable Delivery date, where the delay was not due to an Uncontrollable Event. In the event that ISIS is late in the delivery of API, ISIS will pay, or reimburse LILLY, [***].

5.3 Acceptance and Claims; Materials Review Board.

(a) If LILLY claims that any sample of API did not meet the warranty specified in Article 8, LILLY will notify ISIS in writing within [***] of such Delivery, and a joint Materials Review Board formed under subsection (b) below will review the test data generated by LILLY and ISIS under QA approved procedures mutually agreed by the parties within [***] after LILLY's notice to ISIS.

(b) Promptly after the Effective Date, ISIS and LILLY will each select 2 members of their in-house materials review boards (or other senior personnel with appropriate qualifications) to

participate in a joint Materials Review Board ("MRB") that will review and consider any test data generated by LILLY and ISIS with respect to the Delivered lot of API.

(c) If the members of the MRB are thereafter unable to agree as to whether the API met the warranty specified in Article 8, the parties will cooperate and have the test data reviewed by an independent third party selected by LILLY and approved by ISIS, which approval will not be unreasonably withheld. If the independent third party reviewer cannot determine whether the Delivered API in dispute met the warranty of Article 8, a sample of the lot of the Delivered API in dispute retained by ISIS will be analyzed in accordance with the API Specifications, under QA approved procedures, by an independent testing laboratory of recognized repute selected by LILLY and approved by ISIS, which approval will not be unreasonably withheld. The results of such laboratory testing will be final and binding on the parties on the issue of compliance of the API with such warranty.

(d) If the Delivered API is determined to meet the warranty set forth in Article 8 or fails to meet the warranty as a result of an Uncontrollable Event, LILLY will bear the cost of any third party review and/or independent laboratory testing performed pursuant to subsection (c) above and will pay for the API in accordance with the terms of this Agreement. If the API is determined not to meet the warranty set forth in Article 8 and the reason the API did not meet such warranty was not the result of an Uncontrollable Event, ISIS will bear the cost of any third party review and/or independent laboratory testing performed pursuant to subsection (c) above.

(e) If ISIS agrees, or if it is determined pursuant to subsection (c) above, that API ordered and Delivered at the API Clinical Supply Price did not conform to the warranty set forth in Article 8 and such nonconformance was not the result of an Uncontrollable Event, ISIS will use commercially reasonable efforts to Manufacture and Deliver a replacement lot of API to LILLY for the lot of API that did not conform to such warranty, and LILLY will pay ISIS for any such replacement lot of API, in accordance with the provisions of Section 5.1 herein. [***] In the event of nonconforming API ordered and Delivered at the API Commercial Supply Price and such nonconformance is not the result of an Uncontrollable Event, [***]

(f) Any Delivered API which ISIS agrees did not meet, or which was determined not to have met, the Article 8 warranty that is in LILLY's control will, at ISIS' option, either be returned to ISIS or will be destroyed pursuant to ISIS' instructions and with LILLY's approval, which approval will not be unreasonably withheld, at ISIS' expense.

(g) Failure by LILLY to notify ISIS within [***] after Delivery of API which does not meet the warranty under Article 8 will be a waiver of the remedies available to LILLY under this Section 5.3.

(h) Should either party, or any third party representative of LILLY, identify any possible latent defect of or in API that is not revealed by the procedures set forth above [***] of receipt of any shipment by LILLY, it will so notify the other party immediately upon discovery. LILLY and ISIS will discuss in good faith and agree upon the appropriate measures to be taken by the parties related to such latent defect.

5.4 Terms of Sale.

The terms and conditions of this Agreement will be controlling over any inconsistent terms or conditions included in any agreed-upon order for API or any other sales acknowledgment or document. No provision of any LILLY forms purporting to be orders for API that may impose different conditions than those herein referenced upon ISIS, LILLY or their respective Affiliates will be of any force or effect unless expressly agreed to in writing by both parties.

[***]

(b) This Section 5.5 will survive the termination of this Agreement (other than a termination by LILLY pursuant to Section 13.2(a) for an uncured material breach by ISIS or pursuant to

Section 13.3(b) in the event of an ISIS Change of Control). LILLY's obligations under this Section 5.5 will terminate immediately if the Dedicated Facility is sold, transferred or shut down (except where the Dedicated Facility is shut down because ISIS has no Firm Orders from LILLY outstanding); or ISIS assigns this agreement without LILLY's consent.

5.6 Record Keeping and Audit.

ISIS will keep accurate records in sufficient detail to enable the API Clinical Supply Price, the API Commercial Supply Price [***] to be verified. Upon written request of LILLY and not more than once in each Calendar Year, ISIS will permit representatives of LILLY, including their independent accountants, to have access during normal business hours and upon reasonable advanced written notice to such records as necessary to verify the API Clinical Supply Price, the API Commercial Supply [***] Once specific records have been audited under this Section 5.6, no further audit of such records may be made. If such audit concludes that any amounts are due to either party, such payment will be made within [***] after the determination by the parties. The parties will treat all financial information subject to review under this Section 5.6 in accordance with the confidentiality provisions of the Development and License Agreement, which are incorporated herein and made part of this Agreement by reference. In addition, LILLY will make reasonable efforts to coordinate the timing of audits under this Agreement and the Loan Agreement so as to minimize disruption to ISIS' day-to-day operations.

ARTICLE 6

TECHNOLOGY TRANSFER

6.1 Technology Transfer Team.

(a) The Technology Transfer will be coordinated and implemented under the MWG. The MWG will form a team (the "Technology Transfer Team") comprised of the members of the MWG and such additional employees of each of the parties selected by the MWG as it deems appropriate to effect the Technology Transfer (with equal representation of each of the parties). Members of the Technology Transfer Team will each have appropriate technical credentials, experience and knowledge; the Technology Transfer Team will be co-chaired by a LILLY representative and an ISIS representative from the MWG. The advice of additional employees or consultants of either party may by mutual consent of the parties be obtained.

(b) Decisions of the Technology Transfer Team will be made by unanimous decision of the two-co-chairs; provided however, in the event that the co-chairs do not, after good faith efforts, reach agreement on an issue, the resolution and/or course of conduct in issue will be determined in good faith by the MWG. In the event that the MWG does not, after good faith efforts, reach agreement on such issue, the resolution and/or course of conduct in issue will be determined in good faith by the Product Leader at LILLY with respect to Product, who shall hold at least an Executive Director position at LILLY, after consultation with the Executive Vice President of ISIS.

(c) Throughout the entire Technology Transfer Term, the Technology Transfer Team will meet at least once each month in person or by teleconference, videoconference or by other mutually acceptable means, as necessary to implement effectively and efficiently the Release Technology Transfer Plan and the API Technology Transfer Plan.

6.2 Technology Transfer for Clinical Product Release.

(a) Promptly after the Effective Date, the Technology Transfer Team will establish a plan (the "Release Technology Transfer Plan") for the transfer to LILLY of the Release Technology as specified in the Release Technology Transfer Plan (the "Release Technology Transfer"). The goal of the Release Technology Transfer Plan is to effect the Release Technology Transfer at the same time that LILLY's manufacturing facility becomes available.

(b) The Release Technology Transfer Plan will include *inter alia* (i) procedures designed to effect the prompt and efficient Release Technology Transfer, (ii) a list of events necessary to accomplish the Release Technology Transfer, (iii) a description of the training and support to be provided by ISIS to LILLY during the Release Technology Transfer, and (iv) the time period during which ISIS will perform the Release Technology Transfer.

(c) During the Technology Transfer Term with respect to the Release Technology Transfer, ISIS will (i) disclose and transfer to LILLY all of the Release Technology as specified in the Release Technology Transfer Plan and (ii) provide to LILLY the training and support described in the Release Technology Transfer Plan and in this Agreement.

(d) ISIS will use commercially reasonable efforts to perform the Release Technology Transfer in accordance with the Release Technology Transfer Plan and the terms of this Agreement. The parties will cooperate so that the Release Technology Transfer may be completed as expeditiously as possible.

(e) LILLY will use commercially reasonable efforts to implement the Release Technology to be transferred by ISIS pursuant to this Section 6.2, and to make available all reasonably necessary personnel and other resources to enable such transfer without delay.

6.3 Technology Transfer Plan for Manufacture of API.

(a) Promptly after the Effective Date, the Technology Transfer Team will establish a plan (the "API Technology Transfer Plan") for the transfer of the Manufacturing Process and the Manufacturing Technology for the Manufacture of API from ISIS to LILLY, its Affiliates or a third party designated by LILLY (the "API Technology Transfer"). The goal of the API Technology Transfer Plan is to enable LILLY to apply the Manufacturing Technology, implement the Manufacturing Process and Manufacture API as soon as LILLY's manufacturing facility becomes available.

(b) The API Technology Transfer Plan will include *inter alia* (i) procedures designed to effect the prompt and efficient API Technology Transfer, (ii) a list of events necessary to accomplish the API Technology Transfer, (iii) a description of the training and support to be provided by ISIS to LILLY during the API Technology Transfer, and (iv) the time period during which ISIS will perform the API Technology Transfer.

(c) During the Technology Transfer Term with respect to the API Technology Transfer, ISIS will (i) disclose and transfer to LILLY all of the Manufacturing Process and the Manufacturing Technology as specified in the API Technology Transfer Plan and (ii) provide to LILLY the training and support described in the API Technology Transfer Plan and in this Agreement.

(d) ISIS will use commercially reasonable efforts to perform the API Technology Transfer in accordance with the API Technology Transfer Plan and the terms of this Agreement. The parties will cooperate so that the API Technology Transfer may be completed as expeditiously as possible.

(e) LILLY and/or its third party manufacturer will use commercially reasonable efforts to establish the Manufacturing Process for the Manufacture of API to be transferred by ISIS pursuant to this Section 6.3, and to make available all reasonably necessary personnel and other resources to enable such transfer without delay.

6.4 Training and Support.

The training and support to be provided by ISIS to LILLY in connection with the Release Technology Transfer and the API Technology Transfer (the "Technology Transfer") will include without limitation training and support in a mutually acceptable facility in all of the methods necessary to practice the Release Technology and the Manufacturing Technology, as detailed in the Release Technology Transfer Plan and the API Technology Transfer Plan. In addition, a reasonable number of

employees of LILLY and its Affiliates will be entitled to visit ISIS facilities including without limitation pilot and commercial scale facilities and testing laboratories to observe relevant processes in operation.

6.5 Payment of Technology Transfer Costs.

The Technology Transfer Team will submit a plan for resourcing the Technology Transfer to the MWG. A budget for ISIS and LILLY resources to be used in the performance of the Technology Transfer will be developed to ensure effective forward planning and cost management. LILLY will compensate ISIS by paying [***] ISIS will invoice LILLY on a quarterly basis for all activities performed and expenses incurred in accordance with this Article. LILLY will pay each invoice within [***] after receipt. Interest will be charged on late payments consistent with the provisions of Section 5.1(c).

6.6 Records.

ISIS will maintain records, in sufficient detail and in good scientific manner appropriate for patent, regulatory and manufacturing purposes, which will fully and properly reflect all of the work done and the progress achieved in the performance of the Technology Transfer (the "Records"). The Records at all times will be available to the Technology Transfer Team and LILLY will have the right, during normal business hours and upon reasonable notice, to inspect and copy all such Records. LILLY also will have the right to arrange for its employees and/or consultants to visit ISIS at its offices and laboratories and other facilities during normal business hours on reasonable notice concerning or in furtherance of the Technology Transfer and/or to discuss the progress of the Technology Transfer and its results in detail with the technical personnel and consultants of ISIS.

ARTICLE 7

ISIS CMC AND DEVELOPMENT ACTIVITIES

7.1 ISIS CMC Activities.

(a) As part of its activities under the Development Plan set forth in the Development and License Agreement, ISIS will perform the CMC items set forth in Exhibit 3 hereto. ISIS will perform the listed activities and such other activities as approved by the JDC in support of the preparation and filing of the NDA according to the schedule set forth in the Development Plan.

(b) In consideration of ISIS' performance of CMC activities in connection with ISIS 3521 as set forth in Exhibit 3, LILLY will compensate ISIS for such performance at [***] ISIS will invoice LILLY on a quarterly basis for all activities performed in accordance with this Article and related expenses. Payments due under this Section will be [***] days after receipt of each invoice by LILLY. Interest will be charged on late payments consistent with the provisions of Section 5.1(c).

7.2 ISIS Development Activities.

(a) LILLY will compensate ISIS for additional development efforts undertaken by ISIS, such as analytical methods development for raw materials, API and drug product testing and release, and process development in connection with other phosphorothioate oligodeoxynucleotides, which additional activities support the activities of ISIS with regard to ISIS 3521.

(b) In consideration of ISIS' performance of such additional activities in connection with ISIS 3521, LILLY will compensate ISIS at the [***] used in activities allocated to ISIS 3521 development, manufacture or support, [***] Payments due under this Section will be due [***] days after receipt of each invoice by LILLY. Interest will be charged on late payments consistent with the provisions of Section 5.1(c).

ARTICLE 8

PRODUCT WARRANTY

8.1 API Specifications; cGMPs; Applicable Laws.

Subject to Section 8.2 below, ISIS warrants that the API will, at the time of Delivery, be Manufactured in accordance with and meet (a) the API Specification; (b) cGMP; (c) requirements of the Quality Agreement, (d) the requirements of the MRD, and (e) the Legal Requirements.

8.2 Foreign Manufacturing Requirements.

If the cGMP or the Legal Requirements applicable to the Manufacture of API for use in the U.S. (the "U.S. Manufacturing Requirements") are different from those applicable outside to the Manufacture of API for use in countries other than the U.S. (the "Foreign Manufacturing Requirements"), the warranty of subsection (a) will include such Foreign Manufacturing Requirements only if LILLY has informed ISIS thereof in writing as provided in Section 4.1, the parties have resolved any conflicts as provided in Section 4.6, and have adapted the Manufacturing Process, if necessary, as provided in Section 4.3.

8.3 MRB Approved API.

Notwithstanding anything in this Agreement, API will be deemed to conform with API Specifications at the time of Delivery if approved by the MRB pursuant to Section 5.3 for release and further processing into Product.

ARTICLE 9

QUALITY CONTROL

9.1 Specifications and Process Changes.

The API Specification may not be materially amended, changed or supplemented, except as provided in Section 4.3 and 4.6 above. Unless otherwise specified in that Section, material changes required to comply with applicable laws and regulations and Agency requirements will be mutually agreed upon by ISIS and LILLY.

9.2 Matters Relating to the Facility.

(a) ISIS will Manufacture API supplied by ISIS hereunder at the Dedicated Facility. ISIS will perform release testing of API at the Dedicated Facility and/or the facility of subcontractors.

(b) LILLY will have the right to have a maximum of [***] persons at the Facility while ISIS is conducting development activities, Manufacturing the API for LILLY, or in the event that ISIS fails to supply or is having problems supplying API that meets the API Specifications in a timely manner. LILLY will consult with the MWG on the individuals to be assigned to these positions. ISIS may escort any LILLY visitors to the Facility, and all LILLY visitors will abide by ISIS' safety and other workplace rules, practices and procedures. Observations made by LILLY personnel will be promptly discussed with ISIS and such corrective action as LILLY determines to be reasonably required will be promptly implemented by ISIS at LILLY's expense. ISIS will maintain complete and accurate records of all reasonably relevant information relating to the performance by ISIS of its obligations hereunder. ISIS will permit LILLY to review relevant cGMP documentation. LILLY visitors will maintain as confidential any ISIS Proprietary Information (as defined in the Development Agreement) that they receive or are exposed to which does not directly pertain to this Agreement or the Development Agreement.

9.3 Quality Assurance Audits.

ISIS will perform inspections of its facilities to review its manufacturing operations and assess its compliance with cGMP. In addition, upon LILLY's written request and at mutually agreeable times during normal business hours, ISIS will permit representatives of LILLY to review ISIS' manufacturing operations and records and assess its compliance with cGMP and quality assurance standards and to discuss any manufacturing issues with ISIS' manufacturing and management personnel. Through the MWG, LILLY will have notice of how many production runs ISIS may conduct in a given Calendar Year, which will permit LILLY personnel to observe any such production run, if LILLY so chooses, after providing notice to ISIS (and at its own expense). In the event of a regulatory inspection that directly involves the API, ISIS will immediately inform LILLY of the issuance of the Notice of Inspection (or an equivalent notice from a non-U.S. Regulatory Authority) will provide LILLY with copies of all communications relating thereto and LILLY will be allowed to participate.

9.4 Testing.

(a) ISIS will perform such tests as are indicated in the API Specification. Such testing methods will be qualified by ISIS prior to use and certain of such tests will be stability indicating. No production lot of API will be released for Delivery unless such tests show the API to meet the API Specification. Should any production lot fail to meet API Specification limits, such lot will not be released, unless the failure is identified following release, in which case the identifying party will immediately notify the other party and they will cooperate on the actions to be taken as described in Section 5.3.

(b) ISIS is responsible for obtaining and retaining, at LILLY's expense, the amount of API required for quality control release testing as indicated in the API Specification, as applicable. Such amounts will be retained for a period of not less than 1 year from the last retest date prescribed by ISIS, and thereafter shipped at LILLY's request for longer term storage at a designated LILLY facility.

(c) At LILLY's expense and approval, ISIS will perform an on-going program of stability testing, as required in the stability plan to be agreed by the parties, and provide a stability report to support the transportation of API to a LILLY-designated facility. The stability study period will be for a period specified by LILLY following completion of Manufacture of such production lots and such stability testing will be stability indicating. In the event that ISIS will detect a change in a degradant in excess of the amount specified in the stability plan of API in connection with such testing, ISIS will notify LILLY, and as a part of each stability test of such lot thereafter, ISIS will specifically incorporate additional testing and controls (e.g., storage condition changes), as LILLY may reasonably specify.

(d) In consideration of ISIS' performance of testing as set forth in subsection (c) above, LILLY will compensate ISIS for such performance [***] ISIS will invoice LILLY on a quarterly basis for all activities performed in accordance with this Section 9.4 and related expenses. Payments due under this Section will be due [***] after receipt of each invoice by LILLY. Interest will be charged on late payments consistent with the provisions of Section 5.1(c).

9.5 Information Relating to Manufacturing Conditions.

(a) Each party will notify the other immediately of any health hazards with respect to API of which it becomes aware which may impact employees involved in the Manufacture of API.

(b) Each party will promptly advise the other of any safety or toxicity problem that is not part of the knowledge base readily available in chemical manufacturing facilities of which either party becomes aware regarding the API.

9.6 Agency Inspections.

ISIS hereby agrees to advise LILLY of any visit or inspection by an Agency of the Dedicated Facility relating to the Manufacture of API, provide copies of all communications relating thereto and

will permit one or more qualified representative(s) of LILLY to be present, when possible. If LILLY is not present during such a visit or inspection for any reason, ISIS will promptly provide a copy of the actual report of the results of the inspection to LILLY. ISIS will furnish LILLY copies of all reports, documents or correspondence with respect to any such Agency inspections of the Dedicated Facility.

9.7 Storage and Delivery.

ISIS will store and Deliver API in accordance with the MRD and/or Quality Agreement, API Specifications and label requirements set forth by the MWG and cGMP or applicable Regulatory Approval, as appropriate.

ARTICLE 10

REGULATORY MATTERS

10.1 ISIS will prepare and promptly provide necessary and useful information, including without limitation Manufacturing information, as is needed to support filings of Registrations by LILLY, its Affiliates, sublicensees or distributors of Product. In addition, ISIS will participate as required in resolving regulatory concerns. ISIS will be responsible for maintaining current technical information needed to support such submissions of Registrations, and accordingly will promptly provide LILLY with advance notification of all changes in such technical information required to be filed as amendment to CMC. All such activities will be at LILLY's expense, which will be agreed to in advance by the parties.

10.2 The mutual goal of ISIS and LILLY will be to maintain an integrated approach to the content and timing of all submissions of Registrations made by LILLY in an effort to obtain and maintain regulatory approvals of a Product. To ensure this mutual goal is met, with respect to issues pertaining to API or to a Product, ISIS will provide to LILLY the right to review and reference all authorizations, certificates, methodologies and specifications in the possession or under the control of ISIS relating to the pharmaceutical/technical development and Manufacture or any component thereof to the extent needed for LILLY's filings of Registrations.

ARTICLE 11

RECALLS AND CUSTOMER INQUIRIES

11.1 ISIS and LILLY agree to immediately inform each other in writing of all incidents and/or any Product that is alleged or proved to be the subject of recall, market withdrawal or correction and will cooperate fully with one another in connection therewith. If ISIS or LILLY is required or requested by any governmental authority, or if LILLY (in good faith and in accordance with its corporate policy on recalls) otherwise elects, to recall any Product for any reason, LILLY will be responsible for implementing such recall.

LILLY will conduct, in accordance with its corporate quality assurance procedure regarding recalls, an investigation into each recall conducted. LILLY will notify ISIS promptly in writing of the results of such investigations and ISIS will cooperate fully in completing timely investigations relating to Manufacturing at ISIS.

LILLY will be responsible for all expenses it incurs in connection with any Product recall, unless the defect in the recalled Product is attributable to a failure of API Manufactured by ISIS to meet API Specifications at the time of Delivery and such failure was not the result of an Uncontrollable Event. In case of such a failure, ISIS will (subject to the limitations set forth in Article 14) reimburse LILLY for [***]

11.2 The parties will work together to jointly develop processes and procedures for handling inquiries from customers and adverse drug events with respect to Product. Such processes and procedures will be referenced in the MRD and/or Quality Agreement. LILLY will be responsible for

investigating, responding to customers, and tracking such inquiries and events. ISIS will be responsible for providing reasonable assistance for such investigation and reporting Product complaints and adverse drug events to LILLY.

ARTICLE 12

INDEMNIFICATION AND INSURANCE

12.1 Indemnification.

(a) *Clinical Products.* With respect to Clinical Products, ISIS will defend, indemnify and hold harmless LILLY, its Affiliates and their respective directors, officers, employees and agents, and their respective successors and permitted assigns, from any and all claims, actions, causes of action, liabilities,

losses, damages, costs or expenses, including reasonable attorney's fees, which arise out of or relate to claims that may be brought or instituted against them by third parties to the extent based upon or arising out of (i) the failure by ISIS to meet the warranties set forth in Article 8 (provided such failure does not arise solely from actions of the MWG or an Uncontrollable Event); (ii) a material breach by ISIS of its obligations set forth in this Agreement (provided such breach does not arise solely from actions of the MWG or an Uncontrollable Event); or (iii) gross negligence or willful misconduct of ISIS, its officers, employees and agents in the performance of its obligations hereunder.

With respect to Clinical Products, LILLY will defend, indemnify and hold harmless ISIS, its Affiliates and their respective directors, officers, employees and agents, and their respective successors and permitted assigns, from any and all claims, actions, causes of action, liabilities, losses, damages, costs or expenses, including reasonable attorney's fees, which arise out of or relate to claims that may be brought or instituted against them by third parties to the extent based upon or arising out of (i) a material breach by LILLY of its obligations set forth in this Agreement; (ii) actions of the MWG, except to the extent caused by the negligence or willful misconduct of ISIS; or (iii) gross negligence or willful misconduct of LILLY, its officers, employees and agents in the performance of its obligations hereunder.

(b) *Commercial Products*. With respect to Commercial Products, ISIS will defend, indemnify and hold harmless LILLY, its Affiliates and their respective directors, officers, employees and agents, and their respective successors and permitted assigns, from any and all claims, actions, causes of action, liabilities, losses, damages, costs or expenses, including reasonable attorney's fees, which arise out of or relate to claims that may be brought or instituted against them by third parties to the extent based upon or arising out of (i) the failure by ISIS to meet the warranties set forth in Article 8 (provided such failure does not arise solely from actions of the MWG or an Uncontrollable Event); (ii) a material breach by ISIS of its obligations set forth in this Agreement (provided such breach does not arise solely from actions of the MWG or an Uncontrollable Event); or (iii) gross negligence or willful misconduct of ISIS, its officers, employees and agents in the performance of its obligations hereunder.

With respect to Commercial Products, LILLY will defend, indemnify and hold harmless ISIS, its Affiliates and their respective directors, officers, employees and agents, and their respective successors and permitted assigns, from any and all claims, actions, causes of action, liabilities, losses, damages, costs or expenses, including reasonable attorney's fees, which arise out of or relate to claims that may be brought or instituted against them by third parties to the extent based upon or arising out of (i) this Agreement or (ii) the Manufacture, use, importation, or commercialization (including marketing) of Commercial Products, *except* to the extent such claims are based upon or arise out of (x) the failure by ISIS to meet the warranties set forth in Article 8 (provided such failure does not arise solely from actions of the MWG or an Uncontrollable Event); (y) a material breach by ISIS of its obligations set forth in this Agreement (provided such breach does not arise solely from actions of the MWG or an Uncontrollable Event); or (z) negligence or willful misconduct of ISIS, its officers, employees and agents in the performance of its obligations hereunder.

12.2 Claims.

(a) If a claim is made against a party entitled to indemnification under this Article 11, and if that party intends to seek indemnification with respect thereto under this Article 11, the party seeking indemnification (the "Indemnitee") will promptly notify the indemnifying party (the "Indemnifying Party") of such claim. The Indemnifying Party will defend, negotiate and settle such claim, and the Indemnitee will cooperate with the Indemnifying Party in connection therewith. The Indemnitee may participate in the defense of any claim with counsel of its own choice and at its own expense. Neither party will settle or compromise any such claim without the other party's prior written consent, which consent will not be unreasonably withheld. The indemnity agreement in this Article 11 will not apply to amounts paid in settlement of any claim if such settlement is effected without the consent of the Indemnifying Party, which consent will not be unreasonably withheld. Failure of the Indemnitee to deliver notice to the Indemnifying Party within a reasonable time after becoming aware of a claim will not relieve the Indemnifying Party of any liability to the Indemnitee pursuant to this Article 11, except to the extent such delay prejudices the Indemnifying Party's ability to defend such claim.

12.3 Insurance.

Each party will maintain during the term of this Agreement and for [***] thereafter, at its own expense, (i) commercial general liability insurance, including contractual liability coverage, with a minimum limit of [***] per occurrence and [***] annual aggregate; (ii) property insurance to cover [***] and (iii) statutory workers' compensation coverage as required by law.

ARTICLE 13

TERM AND TERMINATION

13.1 Term.

This Agreement will be effective as of the Effective Date, and unless sooner terminated as provided herein, will continue in effect until December 31, 2005 if the US NDA is filed in 2003, and otherwise until December 31, 2006; *provided, however*, that, so long as an Extension Event continues to exist, until December 31, 2009, LILLY may, in its sole discretion, extend the term of this Agreement for consecutive two-year periods by providing ISIS with written notice of such extension at least 6 months prior to the then scheduled expiration date of this Agreement. The term of this Agreement may be further extended by mutual written agreement of the parties.

13.2 Termination by Either Party.

This Agreement may be terminated with written notice by either party at any time during the term of this Agreement:

(a) if the other party is in breach of its material obligations hereunder and has not cured such breach within [***] after written notice requesting cure of the breach has been given; provided, however, in the event of a good faith dispute with respect to the existence of a material breach, the [***] cure period will be tolled until such time as the dispute is resolved pursuant to Section 14.6; or

(b) upon the filing or institution of bankruptcy, reorganization, liquidation or receivership proceedings by the other party or upon an assignment of a substantial portion of the assets for the benefit of creditors by the other party; provided, however, in the case of any involuntary bankruptcy proceeding such right to terminate will only become effective if the party consents to the involuntary bankruptcy or such proceeding is not dismissed within [***] of the filing thereof.

13.3 Termination For Event of Default or Change of Control.

(a) LILLY may terminate this Agreement if an Event of Default has occurred under the Loan Agreement that has not been cured within [***] of its occurrence.

(b) In the event of an ISIS Change of Control, LILLY may either (i) continue this Agreement with the entity surviving the ISIS Change of Control, or (ii) terminate this Agreement, provided that any Firm Orders (and any obligations directly related thereto under this Agreement) existing at the time of such termination will survive.

13.4 Termination of Development and License Agreement.

This Agreement will automatically terminate in the event the Development and License Agreement is terminated for any reason.

13.5 Payment of Outstanding Debts.

Upon expiration or termination of this Agreement for whatever reason, LILLY and ISIS will settle all outstanding invoices or monies owed to the other party in accordance with the terms of this Agreement.

13.6 Effect of Termination or Expiration.

(a) If this Agreement is terminated by LILLY pursuant to Section 13.2(a) or 13.3(a), all orders will be automatically cancelled and ISIS will terminate the Manufacture of API as soon as practicable. LILLY will have the option but not the obligation to (i) purchase all quantities of API stored at ISIS by paying the API Clinical Supply Price or the API Commercial Supply Price, as applicable, as provided in Section 5.1, and (ii) undertake the Manufacture of API or seek a third party to do such Manufacture. If LILLY undertakes to Manufacture or have Manufactured API, then ISIS will continue the transfer of technology pursuant to Article 6 on an expedited basis, at LILLY's expense.

(b) If this Agreement is terminated by LILLY pursuant to Section 13.2(b), LILLY (i) will purchase all quantities of API stored at ISIS by paying the API Clinical Supply Price or the API Commercial Supply Price, as applicable, as provided in Section 5.1, and (ii) will have the right to undertake the Manufacture of API or seek a third party to do such Manufacture. If LILLY undertakes to Manufacture or have Manufactured API, then ISIS will continue the transfer of technology pursuant to Article 6 on an expedited basis, at LILLY's expense.

(c) If this Agreement is terminated by ISIS pursuant to Section 13.2(a), ISIS will have the option but not the obligation to supply under all outstanding quantities set forth in the most recent Firm Order at the API Clinical Supply Price or the API Commercial Supply Price, as applicable. If ISIS elects to so supply, LILLY's payment obligations relating thereto including, without limitation, those set forth in Section 5.1 will continue to apply until all outstanding obligations of LILLY to ISIS are fulfilled. If LILLY undertakes to Manufacture or have Manufactured API, then ISIS will continue the transfer of technology pursuant to Article 6 at LILLY's expense.

(d) If this Agreement is terminated pursuant to Section 13.4, all outstanding quantities of API set forth in the most recent Firm Order will be automatically cancelled and ISIS will terminate the Manufacture of API as soon as practicable. In addition, LILLY will be responsible for all other Manufacturing costs associated with API pursuant to Section 5.1 at the time of termination. Notwithstanding the foregoing, ISIS will use its best efforts to mitigate any costs payable by LILLY under this Section 13.5(d).

(e) If this Agreement expires pursuant to Section 13.1, LILLY will purchase all API ordered by LILLY during the term of this Agreement. ISIS will Deliver such API in accordance with Section 5.2.

ARTICLE 14

DAMAGE LIMITATIONS

EXCEPT AS EXPRESSLY CONTAINED HEREIN, IN NO EVENT WILL EITHER PARTY HERETO, OR ITS DIRECTORS, OFFICERS, EMPLOYEES, AGENTS OR AFFILIATES BE LIABLE TO THE OTHER PARTY OR SUCH OTHER PARTY'S DIRECTORS, OFFICERS, EMPLOYEES, AGENTS, AFFILIATES OR SUBLICENSEES FOR ANY INDIRECT, CONSEQUENTIAL, INCIDENTAL OR SPECIAL DAMAGES, COSTS OR EXPENSES (INCLUDING, BUT NOT LIMITED TO, LOST PROFITS, LOST REVENUES AND/OR LOST SAVINGS) SUFFERED OR INCURRED BY THE OTHER PARTY, WHETHER BASED UPON A CLAIM OR ACTION OF CONTRACT, WARRANTY, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, ARISING FROM THIS AGREEMENT.

ARTICLE 15

MISCELLANEOUS

15.1 Force Majeure.

Neither party will be held liable or responsible to the other party nor be deemed to have defaulted under or breached the Agreement for failure or delay in fulfilling or performing any term of the Agreement when such failure or delay is caused by or results from causes beyond the reasonable control of the affected party including without limitation embargoes, war, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, or acts of God. The affected party will notify the other party of such force majeure circumstances as soon as reasonably practical and will make every reasonable effort to mitigate the effects of such force majeure circumstances.

15.2 Assignment.

This Agreement will inure to the benefit and be binding upon each party, its successors and assigns. The Agreement may not be assigned or otherwise transferred, nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred by either party without the prior written consent of the other party; provided, however, that either party may, without such consent, assign the Agreement and its rights and obligations hereunder in connection with the transfer or sale of all or substantially all of its assets, or in the event of its merger or consolidation or change in control or similar transaction. Any permitted assignee will assume all obligations of its assignor under the Agreement. Any attempted assignment not in accordance with this Section 15.2 will be void.

15.3 Severability.

In the event any one or more of the provisions contained in this Agreement should be held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein will not in any way be affected or impaired thereby, unless the absence of the invalidated provision(s) adversely affect the substantive rights of the parties. The parties will in such an instance use their best efforts to replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s) which, insofar as practical, implement the purposes of this Agreement.

15.4 Notices.

All notices which are required or permitted hereunder will be in writing and sufficient if delivered personally, sent by facsimile or electronic mail (and promptly confirmed), sent by nationally-recognized

overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

if to ISIS, to:	Isis Pharmaceuticals, Inc. Carlsbad Research Center 2292 Faraday Avenue Carlsbad, CA 92008 Attention: Executive Vice President Fax No.: (760) 931-9639 E-Mail: lparshall@isisph.com
with a copy to:	Attention: General Counsel Fax No.: (760) 603-3820 E-Mail: gbryce@isisph.com
if to LILLY, to:	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 Attention: Affinitac Product Team Leader Fax No.: (317) 277-5912 E-Mail: bpaterson@lilly.com
with a copy to:	Attention: General Counsel Fax No.: (317) 433-3000 E-Mail: rok@lilly.com

or to such other address as the party to whom notice is to be given may have furnished to the other party in writing in accordance herewith. Any such notice will be deemed to have been given when delivered if personally delivered or sent by facsimile or electronic mail on a business day, on the business day after dispatch if sent by nationally-recognized overnight courier and on the third business day following the date of mailing if sent by mail.

15.5 Governing Law.

This Agreement will be governed by and construed in accordance with the laws of the State of Delaware without reference to any rules of conflict of laws.

15.6 Dispute Resolution; Oversight Committee.

The parties recognize that disputes may from time to time arise between the parties during the term of this Agreement. In the event of such a dispute, either party, by written notice to the other party, may have such dispute referred to the Oversight Committee, the function of which is to attempt resolution of any disputes arising under this Agreement by good faith negotiations. The Oversight Committee will endeavor to resolve such disputes within 30 days after such notice is received. The Oversight Committee will be comprised of two designated executive officers (or their successors), one from each party. Said designated officers are as follows:

For ISIS:	Chief Executive Officer
For LILLY:	Executive Vice President

In the event the Oversight Committee is unable to reach consensus, LILLY's Executive Vice President will have final decision-making authority

15.7 Remedies.

In the event the parties are unable to resolve any disputes hereunder pursuant to the dispute resolution measures provided herein, each party may pursue its rights and remedies in law or equity in any court of competent jurisdiction.

15.8 Entire Agreement.

This Agreement, the Development and License Agreement and the Loan Agreement contain the entire understanding of the parties with respect to the license, development and commercialization of Products containing API and the Manufacture and supply of API. All express or implied agreements and understandings, either oral or written, heretofore made by the parties on the same subject matter are expressly superseded by this Agreement, the Development and License Agreement and the Loan Agreement. This Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by both parties hereto. The Confidentiality and Publicity Provisions of Article 4 of the Development and License Agreement are expressly incorporated herein and made a part hereof by reference.

15.9 Headings.

The captions to the several Articles and Sections hereof are not a part of the Agreement, but are merely a convenience to assist in locating and reading the several Articles and Sections hereof.

15.10 Independent Contractors.

It is expressly agreed that ISIS and LILLY will be independent contractors and that the relationship between the two parties will not constitute a partnership, joint venture or agency. Neither ISIS nor LILLY will have the authority to make any statements, representations or commitments of any kind, or to take any action, which will be binding on the other, without the prior consent of the other party.

15.11 Waiver.

The waiver by either party hereto of any right hereunder, or the failure to perform, or a breach by the other party will not be deemed a waiver of any other right hereunder or of any other breach or failure by said other party whether of a similar nature or otherwise.

15.12 Counterparts.

The Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

15.13 Waiver of Rule of Construction.

Each party has had the opportunity to consult with counsel in connection with the review, drafting and negotiation of this Agreement. Accordingly, the rule of construction that any ambiguity in this Agreement will be construed against the drafting party will not apply.

15.14 Survival.

Sections 4.8, 5.1 (b) and (c), 5.5, 5.6, 11, 12, 13, 14, 15 will survive the termination of this Agreement.

IN WITNESS WHEREOF, the parties have executed this Agreement as of the Effective Date.

ELI LILLY AND COMPANY		**ISIS PHARMACEUTICALS, INC.**	
By:	/s/ CHARLES E. GOLDEN	By:	/s/ B. LYNNE PARSHALL
Name:	Charles E. Golden	Name:	B. Lynne Parshall
Title:	*Executive Vice President and Chief Financial Officer*	Title:	*Executive Vice President & CFO*

EXHIBIT 1

Definitions

1.1 **"Affiliate"** with respect to either party means any person, organization, corporation or other business entity (collectively, "Person") controlling, controlled by, or under common control with such party. For purposes of this definition, "control" refers to (a) the possession, directly or indirectly, of the power to direct the management or policies of a Person, whether through the ownership of voting securities, by contract or otherwise, and (b) the ownership, directly or indirectly, of at least 50% of the voting securities or other ownership interest of a Person.

1.2 **"Agency"** means the U.S. Food and Drug Administration. In the event LILLY provides written notice to ISIS that LILLY intends to conduct Development Program activities outside of the United States, the term "Agency" will mean with respect to such activities outside the United States the Regulatory Authority (as defined below) of the country specified in such notice involved in granting any approvals relating to such Development Program activities.

1.3 **"Annual Capacity"** has the meaning set forth in Section 3.1(d).

1.4 **"API"** means the bulk drug substance ISIS 3521 Manufactured under this Agreement and meeting the API Specifications.

1.5 **"API Clinical Supply Price"** means [***] of the API Supply Cost.

1.6 **"API Commercial Supply Price"** means [***]

1.7 **"API Specification"** will mean the specification comprising methods, tests and acceptance criteria or release limits of API, which may be amended from time to time by the MWG. The current API Specification will be included in the MRD. API Specification will also include a deviation from the then current MRD as long as such deviation has been accepted by the MRB.

1.8 **"API Supply Cost"** means the cost of Manufacture of API described in Exhibit 4.

1.9 **"Calendar Quarter"** means each successive period of three (3) months commencing on January 1, April 1, July 1, and October 1, and ending, respectively, on March 31, June 30, September 30, and December 31. For purposes of forecasting and placing orders hereunder, the first quarter in any forecast is the first Calendar Quarter, or part of a calendar Quarter, included in that forecast.

1.10 **"Calendar Year"** means each successive period of 12 months commencing on January 1 and ending on December 31.

1.11 **"cGMP"** means the current good manufacturing practices described in Q7A ICH Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients and 21 CFR Parts 210 *et seq.* as applicable to the Manufacture of API in the U.S., as are in effect on the Effective Date or as may subsequently be modified or supplemented. In the event LILLY provides written notice to ISIS that LILLY intends to conduct the Development Program activities in countries outside of the United States, the term "cGMP" will also include corresponding good manufacturing practices in such countries, provided that to the extent any conflict exists between cGMP applicable in the U.S. and in such countries, the cGMP of the U.S. will apply, unless the parties agree otherwise as provided in Section 4.1, 4.3, 4.6 and 8.2.

1.12 **"Clinical Product"** means a formulated pharmaceutical product containing API in finished form used to conduct clinical trials.

1.13 **"Commercial Product"** means a formulated pharmaceutical product containing API for all uses after the first Marketing Approval for the Product, except as noted in Section 5.1(a).

1.14 **"Combination Product"** means any pharmaceutical product that comprises the API and at least one other active compound(s) and/or ingredients. All references to Product (including Clinical Product and Commercial Product) in this Agreement will be deemed to include Combination Product.

1.15 **"Dedicated Facility"** means the Manufacturing facility to be built by ISIS for the purposes of manufacturing the API in satisfaction of this Agreement.

1.16 **"Deliver" or "Delivery"** means the delivery of API by ISIS to the carrier pursuant to Section 5.2. ISIS will ship API to LILLY or a third party, as directed by LILLY.

1.17 **"Designated Representative"** means an individual identified by either party to be their primary contact for activities under this Agreement.

1.18 **"Development and License Agreement"** means the agreement for the development and commercialization of ISIS 3521 entered into by ISIS and LILLY on August 14, 2001.

1.19 **"Development Plan"** means the plan for the development of ISIS 3521 attached as Exhibit C to the Development and License Agreement.

1.20 **"Development Program"** means the activities undertaken by ISIS and LILLY as set forth in the Development Plan.

1.21 **"Extension Event"** means either [***]

1.22 **"Facilities"** means the Dedicated Facility and the ISIS Facility.

1.23 **"Firm Order"** has the meaning set forth in Section 3.1(b).

1.24 **"FTE"** means the equivalent of the scientific or technical work of at least a total of [***] hours per year on or directly related to the Manufacture, the Technology Transfer, CMC activities or any other activities contemplated under this Agreement, carried out by a qualified employee or Temporary Employee. Scientific or technical work can include, but is not limited to, [***] As used in this definition "Temporary Employee" means an employee hired for a limited period of time and whose total compensation cost is equivalent in cost to an ISIS employee's compensation and benefits package at an equivalent level.

1.25 [***]

1.26 **"ISIS 3521"** means the phosphorothioate oligodeoxyribonucleotide that targets human protein kinase C disclosed and claimed (as SEQ ID NO 2) in U.S. Patent No. 5,703,054.

1.27 **"ISIS Change of Control"** will occur if (a) ISIS consolidates or merges with, or into, any Lilly Competitor, winds up or dissolves (or suffers any liquidation or dissolution) or sells, leases, or otherwise transfers (in one transaction or a series of transactions) all or substantially all of its assets to a Lilly Competitor, or (b) the surviving entity of such transaction does not succeeds to all rights, duties and obligations of ISIS under this Agreement and the Loan Agreement. "Lilly Competitor" means a market or technological competitor of LILLY that has a market capitalization equal of at least [***] of the market capitalization of LILLY at the time of the transaction described above.

1.28 **"ISIS Facility"** means the Manufacturing facilities of ISIS located at 2282 Faraday Avenue, Carlsbad, California that is not the Dedicated Facility.

1.29 **"ISIS FTE Rate"** means [***]

1.30 **"JDC"** means the joint development committee established under the Development and License Agreement.

1.31 **"JVAA Study"** means the Phase III clinical trial conducted by ISIS that is ongoing as of the Effective Date, as further described in the Development Plan.

1.32 **"Legal Requirements"** has the meaning set forth in Section 4.7.

1.33 **"Loan Agreement"** means that certain Loan Agreement between LILLY and ISIS of even date herewith.

1.34 **"Manufacture"** or **"Manufactured"** or **"Manufacturing"** means all operations involved in the manufacturing, quality control testing (including in-process, release and stability testing, if applicable), releasing, packaging and shipping of API under this Agreement.

1.35 **"Manufacturing Process"** means the process steps set forth in master batch records for ISIS 3521 in the version existing as of the Original Effective Date, including reasonable minor variants and extensions of process steps thereof.

1.36 **"Manufacturing Technology"** means any and all scientific and technical data and information including without limitation formulas, methods, techniques, protocols, and processes controlled by ISIS as of the Original Effective Date which are necessary for performing the Manufacturing Process.

1.37 **"Manufacturing Working Group"** or **"MWG"** has the meaning set forth in Section 4.3 herein.

1.38 **"Materials Review Board"** or **"MRB"** has the meaning set forth in Section 5.3(b) herein.

1.39 **"Marketing Approval"** means the act of a Regulatory Authority necessary for the marketing and sale of the Product in a country or regulatory jurisdiction, including, without limitation, the approval of the NDA by the FDA.

1.40 **"MRD"** means the Manufacturing Responsibilities Document for the supply of Commercial Product that includes key contacts, supply chain diagrams, forecasting processes, the details of shipping and receiving, and a process for informing ISIS of the batch numbers and expiration date of Product referencing the batch numbers of API contained therein.

1.41 **"NDA"** means a new drug application or other application filed with the FDA to obtain approval for marketing a Product in the United States, or any future equivalent process.

1.42 **"Out-of-Pocket Expenses"** means reasonable costs, other than labor costs, that are directly related to the activities outlined in the Development Plan and this Agreement, including, but not limited to, costs of travel, supplies, outside services, contractors and consultants.

1.43 **"Original Effective Date"** means August 29, 2001.

1.44 **"Oversight Committee"** has the meaning set forth in Section 14.6 herein.

1.45 **"Product"** means preparation(s) containing API for the treatment of cancer in humans, including Clinical Product, Commercial Product, and Combination Product.

1.46 **"Quality Agreement"** has the meaning set forth in Section 4.4.

1.47 **"Raw Materials"** means any raw materials intended for use in the Manufacture of the Product, including those that may not appear in or remain a part of the Product.

1.48 **"Registrations"** means the technical, medical and scientific licenses, registrations, authorizations and/or approvals of API or Product (including, without limitation, IND, DMF, NDA or other prerequisite manufacturing approvals or authorizations, and marketing authorization based upon such approvals or authorizations) that are required by any national, supranational (e.g., the European Commission or the Council of the European Union), regional, state or local regulatory agency, department, bureau or other governmental entity, as amended or supplemented from time to time.

1.49 **"Regulatory Authority"** means any applicable government regulatory authority involved in granting approvals for the marketing, and/or pricing of a Product worldwide, including without

limitation, in the United States, the Food and Drug Administration ("FDA"), and any successor government authority having substantially the same function, and foreign equivalents thereof.

1.50 **"Regulatory Approval"** means the act of a Regulatory Authority necessary for the Manufacture of Product in a country or regulatory jurisdiction.

1.51 **"Release Technology"** means any and all scientific and technical data and information including without limitation formulas, methods, techniques, protocols, and processes controlled by ISIS as of the Original Effective Date regarding Clinical Product release.

1.52 **"Rolling Production Forecast"** has the meaning set forth in Section 3.1(b) herein.

1.53 **"Technology Transfer"** has the meaning set forth in Section 6.4 herein.

1.54 **"Technology Transfer Team"** has the meaning set forth in Section 6.1 herein.

1.55 **"Technology Transfer Term"** means the time period following the Effective Date, as determined by the Technology Transfer Team, during which the Technology Transfer will take place.

1.56 **"Uncontrollable Event"** means either [***]

1.57 **"Validation"** means cGMP validation of the Dedicated Facility as required for LILLY Third Party Supply Services Quality Control sign off of demonstration and validation lots.

EXHIBIT 2

MANUFACTURING CAPACITY OF ISIS

QUARTERLY CAPACITY FOR API
(AS-IS DRUG)

Capacity Level	Capacity (Kg)	Prepayment Amount
0	[***]	
A		
B		
C		

[***]

Starting January 2003, and annually thereafter, the MWG will calculate and set the Prepayment Amounts to be inserted in the table above. The Prepayment Amounts will be calculated by [***]

As part of ISIS' approved annual operating plan, this Exhibit 2 will be updated to reflect material changes in the Manufacturing Capacity. ISIS agrees that its staffing levels will be consistent with the capacity level forecasted in the current Rolling Production Forecast, taking into consideration recent, current and forecasted production.

EXHIBIT 3

ISIS CMC ACTIVITIES*

Tasks to be completed in the CMC area in support of the ISIS 3521 marketing applications:

[***]

EXHIBIT 4

CALCULATION OF API SUPPLY COST

[***]

EXHIBIT 5

[***]

Exhibit 10.2

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

LOAN AGREEMENT

THIS LOAN AGREEMENT (the "Agreement") is entered into as of the 30th day of September 2002, (the "Effective Date"), by and between Eli Lilly and Company, an Indiana corporation ("Lilly"), and Isis Pharmaceuticals, Inc., a Delaware corporation ("Isis").

RECITALS

1. Lilly and Isis have contemporaneously with the execution of this Agreement entered into a Revised and Restated Supply Agreement (the "Supply Agreement") pursuant to which Isis will supply a certain active pharmaceutical ingredient to Lilly.

2. In order to assure sufficient financial resources to build the manufacturing facility necessary to perform its responsibilities under the Supply Agreement, Isis desires to obtain a loan from Lilly.

3. Lilly is willing to make a loan to Isis in accordance with the terms and conditions set forth herein.

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants and promises contained in this Agreement, the Parties, intending to be fully bound, agree as follows:

ARTICLE I. DEFINITIONS

Section 1.01 Defined Terms. As used in this Agreement, the following terms will have the meanings specified below:

"*Affiliate*" means, when used with respect to a specified Person, another Person that directly or indirectly controls or is controlled by or is under common control with the Person specified.

"*Budget*" has the meaning set forth in Section 2.01.

"*Business Day*" means any day other than a Saturday, Sunday, or day on which banking institutions in New York City are not required to be open.

"*Commitment*" means the obligation of Lilly to make a Loan to Isis in the amount set forth in Section 2.01.

"*Commitment Amount*" has the meaning set forth in Section 2.01.

"*Common Stock*" means the common stock, par value $0.001 per share, of Isis.

"*Covenants*" means the covenants of Isis set forth in Article VI hereof.

"*Debt*" means the total amount of the Loan referred to in Section 2.01, including accrued interest, that remains outstanding at anytime.

"*Dedicated Facility*" means the manufacturing facility to be built by ISIS for the purposes of manufacturing the API in satisfaction of the Supply Agreement.

"*Development Agreement*" means the Development and License Agreement between the parties dated August 14, 2001, or any similar agreement between the parties related to a replacement compound (see Section 3.30 of the Development Agreement).

"*Disbursement*" has the meaning assigned to such term in Section 2.02.

"*Equipment*" means the equipment purchased under the Loan Agreement and specified in Exhibit D attached hereto.

"*Event of Default*" has the meaning assigned to such term in Article VII.

"*Financial Officer*" of any corporation means the chairman, president, chief financial officer, or vice president, finance of such corporation.

"*Fundamental change*" has the meaning assigned to such term in Subsection 2.03(f).

"*Governmental Authority*" means any federal, state, local or foreign court or governmental agency, authority, instrumentality or regulatory body.

"*ISIS Change of Control*" will occur if (a) ISIS consolidates or merges with, or into, any Lilly Competitor, winds up or dissolves (or suffers any liquidation or dissolution) or sells, leases, or otherwise transfers (in one transaction or a series of transactions) all or substantially all of its assets to a Lilly Competitor, or (b) the surviving entity of such transaction does not succeed to all rights, duties and obligations of ISIS under this Agreement and the Loan

Agreement. "Lilly Competitor" means a market or technological competitor of Lilly that has a market capitalization equal to at least [***] of the market capitalization of Lilly at the time of the transaction described above.

"*Loan*" means a loan of money from Lilly to Isis pursuant to this Agreement.

"*Payment Date*" will mean the earliest of: (i) the date of termination of the Supply Agreement under Section 13.2 for material breach by Isis, Section 13.3(a) for an Event of Default or Section 13.3(b) for an Isis Change of Control; or (ii) the date that is the tenth anniversary of the Effective Date, *provided, however*, if any such date specified in (i) or (ii) herein is not a Business Day, the Payment Date will be the first Business Day thereafter.

"*Person*" means any natural person, corporation, business trust, joint venture, association, company, limited liability company, partnership or government or any agency or political subdivision thereof.

"*Principal*" means the Debt, less any accrued interest.

"*Product*" means the compound designated ISIS 3521, or any replacement compound pursuant to Section 3.30 of the Development Agreement.

"*Promissory Note*" has the meaning assigned to such term in Section 2.01.

"*Transactions*" has the meaning assigned to such term in Section 3.02 in relation to Isis and in Section 4.02 in relation to Lilly.

"*Validation*" means cGMP validation of the Dedicated Facility as required for LILLY Third Party Supply Services Quality Control sign off of demonstration and validation lots.

Section 1.02. Terms Generally. The definitions in Section 1.01 will apply equally to both the singular and plural forms of the terms defined. The words "include", "includes" and "including" will be deemed to be followed by the phrase "without limitation".

ARTICLE II. LOAN COMMITMENT, DISBURSEMENTS AND REPAYMENT

Section 2.01. Commitment.

(a) Subject to the terms and conditions of this Agreement and relying on the representations and warranties set forth herein, Lilly agrees to make available to Isis a Loan in the aggregate principal amount of [***] (the "Commitment Amount"). The Loan is intended to cover the total actual costs (including Isis internal labor) Isis incurs to construct, equip and Validate the Dedicated Facility. A budget (the "Budget") for these costs is attached hereto as Exhibit B. The Commitment Amount may be increased only by mutual written agreement of the parties. The Loan will bear interest at a rate of [***] per year compounded [***]. The Loan will be evidenced by a promissory note as hereafter described, prepared in substantially the form attached to this Agreement as Exhibit A and dated as of the date of the first Loan Disbursement and payable to the order of Lilly as described in Section 2.03 (the "Promissory Note").

(b) Isis will have no obligation to perform any work to construct, equip or Validate the Dedicated Facility if (i) such work is not specified in the Budget, (ii) such work is requested by Lilly, and (iii) Isis reasonably believes the performance of such work would cause Isis' costs (including Isis' internal labor) to construct, equip and Validate the Dedicated Facility to exceed the Commitment Amount.

Section 2.02. Loan Disbursements.

(a) Subject to the provisions of Subsection 2.02(b), the Loan will be disbursed by Lilly to Isis in three disbursements (each a "Disbursement"). The first Disbursement will be due within five business days of the Effective Date and will cover the actual cost of the equipment (moveable and nonmoveable) set forth in the Budget as well as the total actual costs (including Isis' internal labor) incurred by Isis through the Effective Date to construct, equip and Validate the Dedicated Facility. The second Disbursement will be due on December 15, 2002 and will cover the actual costs (including Isis' internal labor) incurred by Isis through December 10, 2002 to construct, equip and Validate the Dedicated Facility that were not already covered by the first Disbursement. The third Disbursement will be due within one (1) month following the completion of construction and Validation of the Dedicated Facility and will cover the actual costs (including Isis' internal labor) incurred by Isis through such completion to construct, equip and Validate the Dedicated Facility that were not already covered by an earlier Disbursement. Lilly will be under no obligation whatsoever to make any Disbursements after three (3) months following the completion of construction and Validation of the Dedicated Facility; and (ii) if less than the entire Commitment has been disbursed to Isis by the Payment Date, the Commitment will be deemed reduced to an amount equal to the aggregate amount of any Disbursements made prior to the Payment Date.

(b) Lilly may delay any Disbursement during any period of time that an Event of Default has occurred and has not been corrected by Isis, in which event any such delayed Disbursement will be made by Lilly to Isis on the first Business Day following the date on which the reason for the delay ceases to exist. Should Lilly delay a Disbursement under this Subsection 2.02(b) for any reason other than a breach of a Covenant by Isis, Isis' obligation to supply API under the Supply Agreement shall be postponed until the Disbursement has been made.

(c) On or before the date of the first Disbursement pursuant to Subsection 2.02(a), Isis will deliver to Lilly the Promissory Note and the Financial Officer's certificate called for under Subsection 5.01(c). On or before the date of any subsequent Disbursement pursuant to Subsection 2.02(a), Isis will deliver to Lilly the Financial Officer's certificate called for under Subsection 5.02(c).

(d) Provided the requirements above have been met, Lilly will make each Disbursement to Isis within five (5) days of a request for Disbursement or on the date specified in Section 2.02(a) above,

whichever is later, by transferring the amount of such Disbursement by electronic funds transfer to the following account:

Isis Pharmaceuticals, Inc.
Wells Fargo Bank, 401 B Street, Ste 2201
San Diego, CA 92101
Account Number 4946-033701
ABA Number: 121000248

or such Isis bank account as is from time to time designated by Isis to Lilly in writing.

Section 2.03. Repayment of Loan.

Isis will repay to Lilly the entire unpaid amount of the Debt as follows:

(a) Isis will repay the Debt by paying Lilly an amount equal to the first milestone payment Isis receives from Lilly related [***]. Isis will repay the Debt by paying Lilly an amount equal to the second milestone payment due from Lilly, which will be related[***]; *provided, however* that, in the event that the second milestone payment is [***], then Isis' payment hereunder will equal [***] of the milestone received, and the balance of the outstanding Debt will be paid upon receipt of the next milestone payment from Lilly, unless Isis has already repaid the Debt; and

(b) Starting on the Effective Date, Isis will repay the Debt by paying [***] of the API Supply Cost (as defined in the Supply Agreement) to manufacture API, [***] of Isis' cost (determined on a similar basis) to manufacture any other product (commercial or non-commercial) manufactured for Lilly (including a Product as defined in the Supply Agreement), Isis or any third party, by Isis in the Dedicated Facility. Payments hereunder will be made within [***] days following the end of the calendar quarter in which such amounts accrued. Lilly, or an independent certified public accounting firm of its choice (to the extent that such firm is a nationally recognized independent accounting firm), will have the right to request an audit of the records supporting these payments, at its own expense and on an annual basis, to determine, with respect to any of the two (2) preceding calendar years, the correctness of any report or payment made under this Agreement. The expense of any such audit will be borne by Lilly; provided, however, that if an error in favor of Lilly of more than [***] is discovered, then such expenses shall be paid by Isis. If such audit concludes that any amount is due to either party, such payment will be made within [***] days after receipt of the audit report. The parties will treat all financial information subject to review under this Section 2.03(b) in accordance with the confidentiality provisions in Article 4 of the Development Agreement, which provisions are incorporated herein and made a part of this Agreement by reference.

(c) Until the Debt has been repaid in full, Isis will also continue to make payments under Subsections 2.03(a) and 2.03(b).

(d) All payments made under Subsections 2.03(a) and 2.03(b) above will be made by offsetting the payments due from Lilly against the corresponding payment due from Isis. Any outstanding amount of the Debt will be due and payable, without notice or demand, in its entirety on the Payment Date.

(e) In the event that Isis has not fully repaid the Debt on a Payment Date which results from the tenth anniversary of the Effective Date, then, at Isis' option, Isis will repay the Debt in full by making equal quarterly installments over the two years following the Payment Date using one of the following options. Isis will notify Lilly of how the Debt will be paid at least fifteen (15) days prior to that Payment Date.

(i) Payment in cash;

(ii) Conversion of the Promissory Note into the number of Common Shares equal to the total amount of the Debt being repaid divided by the average closing stock price of the Common Stock

for the thirty (30) days prior to the date of payment. Such stock will be covered by and subject to the Registration Rights and Standstill Agreement, dated August 17, 2001, between the parties. The amount described above will be adjusted to reflect any subdivision of the outstanding shares of Common Stock (by stock split, dividend, or otherwise) or any combination of the outstanding shares of Common Stock into a smaller number of shares occurring during the thirty (30)-day pricing period.

Isis will transfer the number of shares of Common Stock determined as described above on the Payment Date. Isis will notify Lilly of any reclassification of the outstanding shares of Common Stock, or consolidation, merger or share exchange of Isis with another Person, or any other transaction or series of related transactions in which shares of Common Stock are changed into, converted into, or exchanged for other securities or property in each case where Isis is not the surviving entity (each a "Fundamental Change").

No fractional shares will be issued upon conversion of the Promissory Note into shares of Common Stock. If any fractional share of Common Stock would, except for the provisions of this Section, be delivered upon such conversion, Isis, in lieu of delivering such fractional share, will pay to Lilly an amount in cash equal to the fractional share amount times the applicable conversion price.

In the event of conversion of the Promissory Note to Common Stock, Isis will deliver to Lilly an opinion of counsel from Isis' Vice President, Legal and General Counsel, dated as of the Payment Date, in substantially the same form and content as set forth in the attached Exhibit C; or

(iii) Transfer to Lilly of title and possession of the Equipment, without any further notice or action by Lilly. Isis agrees to provide Lilly with reasonable access to the Dedicated Facility during business hours with reasonable prior written notice, and will facilitate the removal of the Equipment from the Dedicated Facility in this event. This transfer of Equipment will equal payment in full on the Debt.

(f) In the event that Isis has not fully repaid the Debt on a Payment Date which results from termination of the Supply Agreement under Section 13.2 for material breach by Isis, Section 13.3(a) for an Event of Default or Section 13.3(b) for an Isis Change of Control, the entire Debt will be due and payable in cash on that Payment Date.

Section 2.04. Payment. All payments under this Agreement shall be made in cash, via wire transfer to the following account:

Mellon Bank
Pittsburgh, PA

ABA 043000261
For Account of: Eli Lilly and Company
Customer Number: 1971431
Ref: ISIS Loan Repayment

or such other account as may be specified by Lilly, unless otherwise expressly agreed between the parties.

Section 2.05. Prepayment.

(a) Isis will have the right at any time, and from time to time, to prepay the Debt in cash prior to the Payment Date, in whole or in part, without penalty upon giving written notice to Lilly before noon Indianapolis time, at least one Business Day prior to prepayment. Prepayments will be in a minimum amount of one million U.S. Dollars ($1,000,000) or in integral multiples thereof, unless such repayment represents the remainder of the balance of the Debt.

(b) Each notice of prepayment will specify the prepayment date and the amount of the Debt to be prepaid, will be irrevocable and will commit Isis to prepay such amount of the Debt as is stated therein on the date specified therein. All prepayments under this Section 2.05 will be made by electronic funds transfer to Lilly's designated account, and will be applied first to any outstanding interest and then any outstanding Principal.

Section 2.06. Release From Liens.

(a) Once Isis has repaid the Debt in full, Lilly will facilitate and take all actions necessary to release the security interest and any related liens on the Equipment.

ARTICLE III. ISIS' REPRESENTATIONS AND WARRANTIES

Section 3.01. Organization and Powers. Isis represents and warrants to Lilly that Isis:

(a) is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware,

(b) has all requisite corporate power and authority to own its property and assets and to carry on its business as now conducted and as proposed to be conducted, and

(c) has the corporate power and authority to execute, deliver and perform its obligations under this Agreement and to borrow hereunder.

Section 3.02. Authorization. Isis represents and warrants to Lilly that the execution, delivery and performance by Isis of this Agreement and the borrowing of the Loan and payment of the Debt (collectively, the "Transactions") (a) have been duly authorized by all requisite corporate action, and (b) will not (i) violate (A) any provision of any law, statute, rule or regulation or of the certificate of incorporation or other constitutive documents or bylaws of Isis; (B) any order of any Governmental Authority; or (C) any provision of any indenture, agreement or other instrument or contract to which Isis is a party; (ii) be in conflict with, result in a breach of, or constitute (alone or with notice or lapse of time or both) a default under, any such indenture, agreement or other instrument; or (iii) result in the creation or imposition of any lien upon any property or assets of Isis except in each case as specified in this Agreement or where such violation, conflict or lien would not materially impede Isis' ability to fully perform its obligations under this Agreement.

Section 3.03. Enforceability. Isis represents and warrants to Lilly that this Agreement constitutes a legal, valid and binding obligation of Isis, enforceable in accordance with its terms (subject, as to enforceability, to applicable bankruptcy, insolvency, reorganization, moratorium or other similar laws affecting creditors' rights generally and to general principles of equity, regardless of whether such enforceability is considered in a proceeding at law or in equity).

Section 3.04. Governmental Approvals. Isis represents and warrants to Lilly that no action, consent or approval of, registration or filing with, or other action by, any Governmental Authority is required in connection with the Transactions.

Section 3.05. Litigation. Isis represents and warrants to Lilly that there are no actions, proceedings or investigations filed or, to the actual knowledge of Isis' chairman of the board, chief executive officer, chief financial officer or general counsel, threatened, against Isis in any court or before any Governmental Authority or arbitration board or tribunal which question the validity or legality of this Agreement, the Transactions or any action taken or to be taken by Isis pursuant to this Agreement and no order or judgment has been issued or entered restraining or enjoining Isis from the execution, delivery or performance of this Agreement.

Section 3.06. Use of Proceeds and Inspection Rights. Isis represents and warrants to Lilly that all proceeds of the Loan will be used solely for equipping, constructing, and Validating the Dedicated Facility (including Isis' internal labor) consistent with the Budget. Isis will maintain accurate records in sufficient detail to reflect the use by Isis of the proceeds from the Loan (including the FTEs hours, by individual, needed to construct, equip and Validate the Dedicated Facility and allocation reconciliation of cost between the Dedicated Facility and the Facility). Each month Isis will provide the MWG (as defined in the Supply Agreement) a report based on such records (in which FTE hours will be reported by department) for the MWG's review and discussion, if any. After Isis has closed its financial books for Isis' 2002 fiscal year, Lilly or an independent certified public accounting firm of its choice (to the extent that such firm is a nationally recognized independent accounting firm), will have [***], during normal business hours, upon reasonable notice, and at Lilly's expense, to audit such records; *provided*, that the parties may mutually agree in writing to forego this [***] and rely on a letter from Isis' independent auditors regarding its audit of such records and the use of the Loan proceeds. If such audit concludes that any amount is due to either party, such payment will be made within thirty (30) days after receipt of the audit report. The parties will treat all financial information subject to review under this Section 2.03(b) in accordance with the confidentiality provisions in Article 4 of the Development Agreement, which provisions are incorporated herein and made a part of this Agreement by reference.

Section 3.07. Solvency. Isis represents and warrants to Lilly that it is not currently insolvent, i.e., unable to pay its debts and obligations as they become due for payment.

ARTICLE IV. LILLY REPRESENTATIONS AND WARRANTIES

Section 4.01. Organization and Powers. Lilly represents and warrants to Isis that Lilly:

(a) is a corporation duly organized, validly existing and in good standing under the laws of the State of Indiana, and

(b) has all requisite corporate power and authority to execute, deliver and perform its obligations under this Agreement.

Section 4.02. Authorization. Lilly represents and warrants to Isis that the execution, delivery and performance by Lilly of this Agreement and the making of the Loan (collectively, the "Transactions") (a) have been duly authorized by all requisite corporate action, and (b) will not (i) violate (A) any provision of any law, statute, rule or regulation or of the certificate of incorporation or other constitutive documents or bylaws of Lilly; or (B) any order of any Governmental Authority; or (C) any provision of any indenture, agreement or other instrument filed as an exhibit to Lilly's reports required to be filed under Section 13 of the Securities and Exchange Act of 1934; (ii) be in conflict with, result in a breach of, or constitute (alone or with notice or lapse of time or both) a default under any such indenture, agreement or other instrument; or (iii) result in the creation or imposition of any lien under any property or assets of Lilly except in each case where such violation, conflict or lien would not materially impede Lilly's ability to fully perform its obligations under this Agreement.

Section 4.03. Enforceability. Lilly represents and warrants to Isis that this Agreement constitutes a legal, valid and binding obligation of Lilly, enforceable in accordance with its terms (subject, as to enforceability, to applicable bankruptcy, insolvency, reorganization, moratorium or other similar laws affecting creditors' rights generally and to general principles of equity, regardless of whether such enforceability is considered in a proceeding at law or in equity).

Section 4.04. Governmental Approvals. Lilly represents and warrants to Isis that no action, consent or approval of, registration or filing with, or other action by, any Governmental Authority is required in connection with the Transactions.

Section 4.05. Litigation. Lilly represents and warrants to Isis that there are no actions, proceedings or investigations filed or, to the actual knowledge of Lilly's chairman of the board, chief executive officer, chief financial officer or general counsel, threatened, against Lilly in any court or before any Governmental Authority or arbitration board or tribunal which question the validity or legality of this Agreement, the Transactions or any action taken or to be taken by Lilly pursuant to this Agreement and no order or judgment has been issued or entered restraining or enjoining Lilly from the execution, delivery or performance of this Agreement.

ARTICLE V. CONDITIONS OF LENDING

Section 5.01. The obligations of Lilly to incur the Commitment set forth in Section 2.01, and to make the first Disbursement pursuant to Section 2.02 of this Agreement are subject to the satisfaction of the conditions that on the date of such Loan Disbursement:

(a) The representations and warranties set forth in Article III will be true and correct in all material respects with the same effect as though made on and as of that date, except to the extent such representations and warranties expressly relate to an earlier date,

(b) No Event of Default will have occurred and be continuing, and

(c) Lilly will have received the signed Promissory Note and a Financial Officer's Certificate of Isis, dated as of no more than five (5) days prior to the planned date of the Disbursement, confirming compliance with the conditions precedent set forth in paragraphs (a) and (b) above.

Section 5.02. The obligations of Lilly to make Loan Disbursements subsequent to the first Disbursement pursuant to Section 2.02 of this Agreement are subject to the satisfaction of the conditions that on the date of each subsequent Loan Disbursement:

(a) The representations and warranties set forth in Article III will be true and correct in all material respects with the same effect as though made on and as of that date, except to the extent such representations and warranties expressly relate to an earlier date,

(b) No Event of Default will have occurred and be continuing, and

(c) Lilly will have received a Financial Officer's Certificate of Isis, dated as of no more than five (5) days prior to the planned date of the Disbursement, confirming compliance with the conditions precedent set forth in paragraphs (a) and (b) above.

ARTICLE VI. ISIS COVENANTS

Section 6.01. Isis hereby grants to Lilly a continuing security interest in the Equipment. Isis covenants and agrees that so long as this Agreement remains in effect or the Debt is unpaid, unless Lilly otherwise consents in writing, Lilly will have a lien on the Equipment and Isis will not create nor allow to be created any other lien or security interest in the Equipment. Isis agrees to promptly perform, on request of Lilly, such acts as Lilly may determine to be necessary and advisable to create, perfect, maintain, preserve, protect and continue the perfection of any lien and security interest provided for in this Agreement or otherwise to carry out the intent of this Agreement.

Section 6.02. Isis covenants and agrees with Lilly that so long as this Loan Agreement remains in effect or the Debt is unpaid, unless Lilly otherwise consents in writing, the Dedicated Facility and the Equipment will be used exclusively for manufacture under the Supply Agreement and/or manufacture of other Lilly compounds. During this period Isis will not use the Dedicated Facility or the Equipment for its own benefit or the benefit of a third party in any manner whatsoever without Lilly's prior written consent.

ARTICLE VII. EVENTS OF DEFAULT

An "Event of Default" includes any of the following:

(a) failure by Isis to tender payment of the Debt when and as the same becomes due and payable;

(b) claim of excuse due to a force majeure event under Section 15.1 of the Supply Agreement for a period of more than [***];

(c) breach by Isis of a Covenant set forth in Article VI above; or

(d) termination of the Supply Agreement for material breach by Isis.

ARTICLE VIII. SUBORDINATION

Section 8.01. Subordination of Indebtedness. The parties acknowledge and agree that the obligations evidenced by the Promissory Note and pursuant to this Agreement are, except to the extent of the value of the Equipment, hereby made expressly subordinate and subject in right of payment to the prior payment in full of all principal, interest and other charges relating to or arising under all obligations of Isis for borrowed money or other similar obligations now existing, except for any such obligations arising in connection with a collaboration with a third party pharmaceutical or biotechnology company, which may be *pari passu* with the obligations evidenced by the Promissory Note and pursuant to this Agreement. The parties hereto further expressly acknowledge and agree that the obligations of Isis evidenced by the Promissory Note and this Agreement rank, except to the extent of the value of the Equipment, *pari passu* with the obligations of Isis under that certain Convertible Promissory Note issued by Isis to Elan International Services, Ltd. on April 20, 1999. Notwithstanding the provisions of this Article VIII, Isis' failure to pay the Debt on the Payment Date will constitute a material breach of this Agreement by Isis, and Lilly may pursue any legal remedy available to it in relation to such material breach.

ARTICLE IX. MISCELLANEOUS

Section 9.01. Notices. Except as otherwise expressly provided herein, notices and other communications provided for herein will be in writing and will be delivered by hand or overnight courier service or sent by telecopy, as follows:

(a) If to Isis

2292 Faraday Avenue
Carlsbad, CA 92008
Attention: Chief Financial Officer
Tel: 760-603-2460
Fax: 760-931-9639

with a copy to:

2292 Faraday Avenue
Carlsbad, CA 92008
Attention: Vice President Legal, General Counsel
Tel: 760-931-9200
Fax: 760-268-4922

(b) If to Lilly:

Eli Lilly and Company
Lilly Corporate Center

Indianapolis, IN 46285
Fax: 317-433-3000
telephone confirmation required at 317-276-2703
Attention: Rebecca O. Kendall, Esq., Senior Vice President and
General Counsel

with a copy to:

Fax: 317-277-5912
telephone confirmation required at 317-276-9115
Attention: Affinitac Product Team Leader

All notices and other communications given to any Party hereto in accordance with the provisions of this Agreement will be deemed to have been given on the date of receipt if delivered by hand or overnight courier service or sent by telecopy to such Party as provided in this Section or in accordance with the latest unrevoked direction from such Party given in accordance with this Section.

Section 9.02. Survival of Agreement. All covenants, agreements, representations and warranties made by Isis herein and in the certificates or other instruments prepared or delivered in connection with or pursuant to this Agreement will be considered to have been relied upon by Lilly and will survive the making by Lilly of the Commitment set forth in Section 2.01 regardless of any investigation made by Lilly, and will continue in full force and effect as long as the Debt or any other amount payable under this Agreement is outstanding and unpaid or the Commitment has not been terminated.

Section 9.03. Successors and Assigns.

(a) Neither Party will assign or delegate any of its rights and duties hereunder without the prior written consent of the other Party, and any attempt so to assign or delegate will be void, except that Lilly may assign its rights and obligations hereunder, in whole or in part, to an Affiliate without the approval or consent of Isis; provided that Lilly will remain liable for all funding obligations hereunder;

(b) Subject to Subsection 9.03(a), whenever in this Agreement one of the Parties hereto or thereto is referred to, such reference will be deemed to include the permitted successors and assigns of such Party, and all covenants, promises and agreements by or on behalf of a Party that are contained in this Agreement will bind and inure to the benefit of its permitted successors and assigns.

Section 9.04. Applicable Law. All questions concerning the construction, validity and interpretation of this Agreement will be construed in accordance with and governed by the laws of the State of Delaware without regard to principles of conflicts of laws.

Section 9.05. Waivers: Amendment.

(a) No failure or delay of Lilly in exercising any power or right hereunder will operate as a waiver thereof, nor will any single or partial exercise of any such right or power, or any abandonment or discontinuance of steps to enforce such a right or power, preclude any other or further exercise thereof or the exercise of any other right or power. The rights and remedies of Lilly hereunder are cumulative and are not exclusive of any rights or remedies which it would otherwise have. No waiver of any provision of this Agreement or consent to any departure therefrom will in any event be effective unless the same is permitted by Subsection (b) below, and then such waiver or consent will be effective only in the specific instance and for the purpose for which given.

(b) Neither this Agreement nor any provision hereof may be waived, amended or modified except pursuant to an agreement or agreements in writing entered into by Isis and Lilly.

Section 9.06. Severability. In the event any one or more of the provisions contained in this Agreement should be held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein will not in any way be affected or impaired

thereby. The parties will endeavor in good faith negotiations to replace the invalid, illegal or unenforceable provisions with valid provisions the economic, and legal, effect of which comes as close as possible to that of the invalid, illegal or unenforceable provisions.

Section 9.07. Counterparts. This Agreement may be executed in two or more counterparts, each of which will constitute an original but all of which when taken together will constitute but one contract.

Section 9.08. Headings. Article and Section headings used herein are for convenience only, and do not constitute a part of this Agreement.

Section 9.09. Right of Setoff. In addition to Lilly's rights of set off described in Section 2.03(d), Lilly is hereby authorized at any time and from time to time, to the fullest extent permitted by law, to set off and apply the monetary obligations owing by Lilly to Isis under Section 5.5 of the Supply Agreement against any outstanding Debt. In addition, if Isis fails to pay the Debt when due as described herein, and such failure continues for more [***] then Lilly is hereby authorized at any time and from time to time, so long as Isis fails to pay the Debt when due, to the fullest extent permitted by law, to set off and apply any and all monetary obligations owed by Lilly to Isis at any time under the Supply Agreement against any outstanding Debt; provided, that Lilly may not off set any monetary obligations that are the subject of a good faith dispute among the parties. Lilly agrees promptly to notify Isis after such setoff and application, but the failure to give such notice will not affect the validity of such setoff and application. Except as described in Section 2.03(d) and this Section 9.09, Lilly will have no other rights of setoff, however the rights of Lilly under this Section are in addition to other rights and remedies it may have.

Section 9.10. Confidentiality and Nondisclosure. The parties agree that the existence and terms of this Agreement are confidential and that neither party will disclose any information related to this Agreement to any third party, nor use such information for any purpose other than those contemplated by this Agreement or as required by law.

IN WITNESS WHEREOF, the parties hereto have caused this Agreement to be duly executed by their respective authorized officers as of the day and year first above written.

ELI LILLY AND COMPANY

By: /s/ CHARLES E. GOLDEN

Name: Charles E. Golden

Title: *Executive Vice President and Chief Financial Officer*

ISIS PHARMACEUTICALS, INC.

By: /s/ B. LYNNE PARSHALL

Name: B. Lynne Parshall

Title: *Executive Vice President & CFO*

EXHIBIT A

THIS SUBORDINATED PROMISSORY NOTE HAS NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933. NO SALE OR DISPOSITION MAY BE EFFECTED EXCEPT IN COMPLIANCE WITH RULE 144 UNDER SAID ACT OR AN EFFECTIVE REGISTRATION STATEMENT RELATED THERETO OR AN OPINION OF COUNSEL FOR THE HOLDER, SATISFACTORY TO THE COMPANY, THAT SUCH REGISTRATION IS NOT REQUIRED UNDER THE ACT OR RECEIPT OF A NO-ACTION LETTER FROM THE SECURITIES AND EXCHANGE COMMISSION.

SUBORDINATED PROMISSORY NOTE

[***] , 2002

San Diego, California

FOR VALUE RECEIVED, ISIS PHARMACEUTICALS, INC., a Delaware corporation ("***Borrower***"), hereby promises to pay to the order of **ELI LILLY AND COMPANY**, an Indiana corporation ("***Lender***"), in lawful money of the United States of America and in immediately available funds, the principal sum [***] (the "***Loan***") together with accrued and unpaid interest thereon, each due and payable on the dates and in the manner set forth in the Loan Agreement (as defined below).

This Subordinated Promissory Note (this "***Note***") is the promissory note referred to in and is executed and delivered in connection with the Loan Agreement between the parties, dated as of September, 2002 and executed by Borrower and Lender (as the same may from time to time be amended, modified or supplemented or restated, the "***Loan Agreement***"). All capitalized terms used herein and not otherwise defined herein will have the respective meanings given to them in the Loan Agreement.

(1) **Loan Requests.** Loan Disbursements made under this Note will be disbursed in the manner and as provided in Section 2.02 of the Loan Agreement. At the time of any borrowing under this Note (or at the time of receipt of any payment of principal or conversion of this Note into equity securities of the Borrower), Lender will make or cause to be made, an appropriate notation on the Exhibit A attached hereto reflecting the amount of such borrowing (or the amount of such payment or conversion). The outstanding amount of this Note set forth on such Exhibit A will be prima facie evidence of the principal amount thereof outstanding, but the failure to record, or any error in so recording, will not limit or otherwise affect the obligations of Borrower to make payments of principal of or interest on this Note when due. Borrower and Lender acknowledge that the initial principal amount outstanding under this Note as of the date hereof will be Dollars ($), as indicated on the attached Exhibit A.

(2) **Interest.** The Loan outstanding from time to time from and after the Effective Date will bear interest as provided in Section 2.01 of the Loan Agreement.

(3) **Repayment.** This Note will be paid as set forth in Section 2.03 of the Loan Agreement.

(4) **Subordination.** The indebtedness evidenced by this Note is hereby expressly subordinated, to the extent, in the manner and to the indebtedness as set forth in Section 8.01 of the Loan Agreement.

(5) **Waiver.** Borrower waives presentment and demand for payment, notice of dishonor, protest and notice of protest of this Note, and will pay all costs of collection when incurred, including, without limitation, reasonable attorneys' fees, costs and other expenses.

(6) **Governing Law.** This Note is governed by, and construed and enforced in accordance with, the laws of the State of Delaware, excluding conflict of laws principles that would cause the application of laws of any other jurisdiction.

ELI LILLY AND COMPANY

By: _____

Printed Name: _____

Title: _____

ISIS PHARMACEUTICALS, INC.

By: _____

Printed Name: _____

Title: _____

PRINCIPAL BORROWINGS SCHEDULE

Date	Borrowing	Repayment	Principal Balance
	$ [ ]		

EXHIBIT B

BUDGET

[***]

EXHIBIT C

Opinion of Counsel

(a) Isis is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware and has full corporate power and authority to conduct its business as presently conducted.

(b) The Common Stock to be issued has been duly authorized and is duly and validly issued, fully paid and non-assessable and free of statutory pre-emptive rights.

(c) The issuance of the Common Stock pursuant to the conversion provisions in the Loan Agreement will not conflict with, or result in any breach of any of the terms, conditions, or provisions of, or constitute a default under, (i) the Certificate of Incorporation or Bylaws of Isis or (ii) any provision of California or federal law, statute, rule or regulation or any provision of the Delaware General Corporation Law.

(d) Except as obtained and in effect on the date of issuance of the Common Stock, no consent, approval, order or authorization of, or registration, qualification, designation, declaration, or filing with, any governmental authority is required on the part of Isis in connection with the issuance of the Common Stock pursuant to the conversion of the Loan Agreement.

EXHIBIT D

Equipment List

[***]

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Exhibit 10.3

AMENDMENT NO. 1 TO
ISIS PHARMACEUTICALS, INC.
10B5-1 TRADING PLAN

This Amendment No. 1 to 10b5-1 Trading Plan (the "Amendment"), is effective as of June 7, 2002 ("Effective Date") between **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation ("Isis"), and **GOLDEN TRIANGLE SECURITIES LLC** ("Broker").

A. WHEREAS, Isis and Broker entered into that certain 10b5-1 Trading Plan dated February 22, 2002 (the "Original Agreement"); and

B. WHEREAS, Isis and Broker wish to amend the Original Agreement to limit Broker's ability to exercise and hold stock options.

NOW THEREFORE, in consideration of the mutual promises contained in this Amendment, Isis and Broker agree to amend the Original Agreement as follows:

All capitalized terms not otherwise defined herein, will have the meanings ascribed to them in the Original Agreement.

ARTICLE 1. AMENDMENT

1.1 *Addition of Section 4(l).* The Original Agreement is hereby amended to include the following language as Section 4(l) thereto:

> "(l) Unless a Seller's Sellers Plan explicitly instructs Broker to do otherwise, if Broker exercises an option because such Option was about to expire, Broker must sell the shares of Stock issued upon the exercise of such Option within 5 Trading Days of exercise at the then prevailing market price for the Stock, regardless of the Minimum Sales Prices set forth in the applicable Sellers Plan."

ARTICLE 2. GENERAL PROVISIONS

2.1 *Original Agreement.* Except as specifically provided in this Amendment, all other terms and conditions of the Original Agreement will remain in full force and effect.

2.2 *Entire Agreement.* This Amendment, the Original Agreement and the Sellers Plans contain the entire understanding of the parties with respect to the subject matter hereof and thereof and supersede all prior agreements and understandings among the parties with respect thereto.

2.3 *Other General Provisions.* Section 6 of the Original Agreement, will apply to this Amendment.

IN WITNESS WHEREOF, the parties hereto have executed this Amendment as of the date first written above:

ISIS PHARMACEUTICALS, INC.

/s/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President

GOLDEN TRIANGLE SECURITIES LLC

/s/ STEVEN HOLBER

Steven Holber
President

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Exhibit 10.3

AMENDMENT NO. 1 TO ISIS PHARMACEUTICALS, INC. 10B5-1 TRADING PLAN

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Exhibit 99.1

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 June 30, 2002, to which this Certification is attached as Exhibit 99.1 (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 14, 2002

/s/ STANLEY T. CROOKE	/s/ B. LYNNE PARSHALL
Stanley T. Crooke, M.D., Ph.D. *Chief Executive Officer*	B. Lynne Parshall, Esq. *Chief Financial Officer*

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Exhibit 99.1

CERTIFICATION