UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549

Form 10-Q

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

For the Quarterly Period Ended September 30, 2006

OR

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

For the transition period from to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.
(Exact name of Registrant as specified in its charter)

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

1896 Rutherford Road, Carlsbad, CA 92008
(Address of principal executive offices, including zip code)

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

Securities registered pursuant to Section 12(b) of the Act: **None**

Securities registered pursuant to Section 12(g) of the Act:
Common Stock, $.001 Par Value

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

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer or a non-accelerated filer (as defined in Rule 12b-2 of the Exchange Act): Large Accelerated Filer o Accelerated Filer x Non-Accelerated Filer o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12(b)-2 of the Securities Exchange Act of 1934). Yes o No x

The number of shares of voting common stock outstanding as of November 2, 2006 was 75,906,739.

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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TRADEMARKS

Macugen® is a registered trademark of Eyetech Pharmaceuticals, Inc.
Vitravene® is a registered trademark of Novartis AG.
Affinitak™ is a trademark of Eli Lilly and Company.
Ibis Biosciences™ is a trademark of Isis Pharmaceuticals, Inc.
Ibis T5000™ is a trademark of Isis Pharmaceuticals, Inc.

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

	September 30, 2006 (Unaudited)	December 31, 2005
ASSETS		
Current assets:		
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $58.6 million and $0 at September 30, 2006 and December 31, 2005, respectively)	$ 104,238	$ 50,885
Short-term investments	22,633	43,504
Contracts receivable	2,959	3,918
Inventory	632	951
Other current assets	6,461	6,600
Total current assets	136,923	105,858
Property, plant and equipment, net	7,227	9,130
Licenses, net	22,018	23,770
Patents, net	17,042	18,773
Deposits and other assets	2,433	3,201
Long-term investments	2,125	5,641
Total assets	$ 187,768	$ 166,373
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,003	$ 2,095
Accrued compensation	1,332	3,706
Accrued liabilities	6,846	8,643

Current portion of long-term obligations	7,684	7,835
Current portion of deferred contract revenue	571	1,514
Total current liabilities	19,436	23,793
5 1/2% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	9,736	14,915
Total liabilities	154,172	163,708
Noncontrolling interest in Symphony GenIsis, Inc	32,019	—
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 73,904,881 and 72,201,505 shares issued and outstanding at September 30, 2006 and December 31, 2005, respectively	74	72
Additional paid-in capital	802,063	770,263
Accumulated other comprehensive income	2,045	3,178
Accumulated deficit	(802,605)	(770,848)
Total stockholders' equity	1,577	2,665
Total liabilities, noncontrolling interest and stockholders' equity	$ 187,768	$ 166,373

See accompanying notes.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Revenue:				
Research and development revenue under collaborative agreements	$ 2,469	$ 7,122	$ 11,260	$ 24,695
Licensing and royalty revenue	784	336	1,327	797
Total revenue	3,253	7,458	12,587	25,492
Operating expenses:				
Research and development	18,973	18,212	56,327	61,523
Selling, general and administrative	2,823	1,724	8,099	5,771
Compensation expense/(benefit) related to variable accounting of stock options	—	15	—	(613)
Restructuring activities	(279)	(349)	(457)	7,385
Total operating expenses	21,517	19,602	63,969	74,066
Loss from operations	(18,264)	(12,144)	(51,382)	(48,574)
Other income (expenses):				
Investment income	1,682	1,241	3,837	2,095
Interest expense	(2,256)	(4,269)	(6,816)	(18,009)
Gain on investments, net	—	—	2,263	—
Net loss before noncontrolling interest in Symphony GenIsis, Inc.	(18,838)	(15,172)	(52,098)	(64,488)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	6,733	—	20,341	—
Net loss applicable to common stock	$ (12,105)	$ (15,172)	$ (31,757)	$ (64,488)
Basic and diluted net loss per share	$ (0.16)	$ (0.24)	$ (0.44)	$ (1.08)
Shares used in computing basic and diluted net loss per share	73,588	64,086	72,934	59,734

See accompanying notes.

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

	Nine Months Ended September 30,

	2006	2005
Net cash used in operating activities	$ (44,354)	$ (47,373)
Investing activities:		
Purchase of short-term investments	(38,468)	(8,466)
Proceeds from the sale of short-term investments	60,000	36,778
Purchase of property, plant and equipment	(1,103)	(397)
Proceeds from the sale of property, plant and equipment	—	8,206
Other assets	(1,293)	(2,787)
Strategic investments	4,397	—
Net cash provided by investing activities	23,533	33,334
Financing activities:		
Net proceeds from issuance of equity	9,021	49,169
Proceeds from long-term borrowings	—	4,603
Principal payments on debt and capital lease obligations	(5,797)	(13,761)
Proceeds from purchase of noncontrolling interest in Symphony GenIsis, Inc., net of fees	70,950	—
Net cash provided by financing activities	74,174	40,011
Net increase in cash and cash equivalents	53,353	25,972
Cash and cash equivalents at beginning of period	50,885	27,250
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $58.6 million and $0 at September 30, 2006 and December 31, 2005, respectively) at end of period	$ 104,238	$ 53,222
Supplemental disclosures of cash flow information:		
Interest paid	$ 4,653	$ 5,018
Warrant issued in conjunction with Symphony GenIsis, Inc. transaction	$ 18,590	$ —

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED CONSOLIDATED FINANCIAL STATEMENTS
September 30, 2006
(Unaudited)

1. Basis of Presentation

The unaudited interim condensed consolidated financial statements for the three and nine month periods ended September 30, 2006 and 2005 have been prepared on the same basis as the audited financial statements for the year ended December 31, 2005. The financial statements include all normal recurring adjustments, which Isis considers necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2005 included in Isis' Annual Report on Form 10-K and 10-K/A filed with the Securities and Exchange Commission ("SEC").

The condensed consolidated financial statements include the accounts of Isis and its wholly-owned subsidiaries, Isis Pharmaceuticals Singapore Pte. Ltd., Isis USA Ltd., Hepasense, Ltd., Orasense, Ltd. and Ibis Biosciences, Inc. On July 25, 2005, Isis dissolved its Hepasense, Ltd. subsidiary. On October 25, 2006, Isis dissolved its Orasense, Ltd. subsidiary. In addition to its wholly-owned subsidiaries, the condensed consolidated financial statements include one variable interest entity, Symphony GenIsis, Inc., for which Isis is the primary beneficiary as defined by Financial Accounting Standards Board Interpretation No. 46 (revised 2003), *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51* ("FIN 46R"). All significant intercompany balances and transactions have been eliminated.

2. Significant Accounting Policies

Revenue Recognition

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

Research and development revenue under collaborative agreements

Isis recognizes research and development revenue under collaborative agreements as it incurs the related expenses, up to contractual limits. Isis defers payments received under these agreements that relate to future performance and records revenue as Isis earns it over the specified future performance period. Isis recognizes revenue that relates to nonrefundable, upfront fees over the period of the contractual arrangements as Isis satisfies its performance obligations. Isis recognizes revenue that relates to milestones, under existing arrangements, upon completion of the milestone's performance requirement. Isis recognizes revenue from arrangements entered into subsequent to June 30, 2003 in accordance with Emerging Issues Task Force Issue No. 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables* ("EITF 00-21"). This issue addresses the timing and method of revenue recognition for revenue arrangements that include the delivery of more than one product or service. Isis sometimes enters into revenue arrangements that contain multiple deliverables. In these cases, Isis recognizes revenue from each element of the arrangement as long as Isis can determine a separate value for each element, Isis has completed its obligation to deliver or perform on that element, and Isis is reasonably assured of collecting the resulting receivable. Isis records revenue from government research grants and contracts during the period in which it incurs the related expenditures. Isis recognizes revenue from product sales as it ships the products.

Isis has implemented the provisions of Staff Accounting Bulletin No. 104, *Revenue Recognition* ("SAB 104"), which was issued in December 2003. SAB 104 updates portions of the interpretive guidance included in Topic 13 of the codification of SAB 101, *Revenue Recognition in Financial Statements*, in order to make this interpretive guidance consistent with current authoritative accounting guidance and SEC rules and regulations. SAB 104 provides interpretation on selected revenue recognition issues and when revenue is properly recognizable. Revenue should not be recognized until it is realized or realizable and earned. It must meet the following criteria: 1) persuasive evidence of an arrangement exists, 2) delivery occurred or services were rendered, 3) the seller's price to the buyer is fixed or determinable and 4) collectibility is reasonably assured.

As part of Isis' Eli Lilly and Company ("Lilly") alliance, in 2001 Lilly provided Isis a $100 million interest-free

loan to fund the companies' joint research collaboration. Isis discounted the loan amounts to their 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 accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to Isis to help fund the research collaboration. Isis accounted for this difference as deferred revenue and recognized it as revenue over the period of performance. In August 2005, in accordance with its terms, Isis converted this loan into 2.5 million shares of its common stock. Concurrent with the conversion, Isis extended the research collaboration.

Licensing and royalty revenue

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

Concentration of Credit Risk

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

Cash, Cash Equivalents and Investments

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Cash and cash equivalents held by Symphony GenIsis primarily consist of investments in money market funds. Isis' short-term investments have initial maturities of greater than ninety days from date of purchase. Isis classifies its securities as "available-for-sale" in accordance with Financial Accounting Standards Board No. 115, *Accounting for Certain Investments in Debt and Equity Securities* ("SFAS 115"). Isis carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal quarter. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses for securities sold in investment income.

In addition to investments in marketable securities, Isis has equity investments in privately- and publicly-held biotechnology companies. Isis holds ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below cost in Isis' equity positions is other-than-temporary, Isis examines historical trends in the stock price, the financial condition of the issuer and the near term prospects of the issuer. When Isis determines that a decline in value is other-than-temporary, Isis recognizes an impairment loss in the period in which the other-than-temporary decline occurs. During the second quarter of 2006, Isis recorded a net gain on investments. This net gain on investments consisted of a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam Pharmaceuticals, Inc. that Isis owns offset by a non-cash loss on investment of $465,000 related to the impairment of Isis' equity investment in Antisense Therapeutics Ltd. ("ATL").

Valuation of Inventory

Isis includes in inventory raw material costs for drugs that Isis manufactures for its partners under contractual terms, and that it uses primarily in its clinical development activities and drug products. Isis expenses these costs when it delivers its drugs to partners, or as it uses these drugs in its own clinical trials. Isis reflects its inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. Isis reviews inventory periodically and reduces its carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. Isis considers several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for its drugs and clinical trial materials and historical write-offs. Total inventory, which consisted solely of raw materials, was $632,000 and $951,000 as of September 30, 2006 and December 31, 2005, respectively.

Licenses

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

Patents

Isis capitalizes costs consisting principally of outside legal costs and filing fees related to obtaining patents. Isis reviews its capitalized patent costs regularly to determine that they include costs for patent applications that have future value. Isis evaluates costs related to patents that it is not actively pursuing and writes off any of these costs, if appropriate, which was $2.2 million and $923,000 for the first nine months of 2006 and 2005, respectively. The charge in 2005 primarily related to restructuring activities. Isis amortizes patent costs over their estimated useful lives of ten years, beginning with the date the patents are issued.

Fair Value of Financial Instruments

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

Long-Lived Assets

Pursuant to the provisions of SFAS 144, *Accounting for the Impairment of Long-Lived Assets*, Isis evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, on at least a quarterly basis, and when events and circumstances indicate that these assets may be impaired. In the first nine months of 2006 and 2005, Isis incurred charges of $2.2 million and $14.8 million, respectively, related to the write-down of equipment and intangible assets to their estimated net realizable values. The charge in 2005 was primarily related to Isis' restructuring activities, which were primarily related to the sale of three of Isis' buildings.

Use of Estimates

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

Consolidation of Variable Interest Entities

Isis has implemented the provisions of FIN 46R, which addresses consolidation by business enterprises of variable interest entities either: (1) that do not have sufficient equity investment at risk to permit the entity to finance its activities without additional subordinated financial support, or (2) in which the equity investors lack an essential characteristic of a controlling financial interest. As of September 30, 2006, Isis had collaborative arrangements with five entities that it considers to be variable interest entities ("VIE") under FIN 46R.

In April 2006, Isis entered into a collaboration with Symphony Capital Partners, L.P. and a group of co-investors to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program. Symphony Capital formed Symphony GenIsis, Inc., capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis treats Symphony GenIsis as a VIE for which Isis is the primary beneficiary. As a result, beginning in the second quarter of 2006, Isis includes the financial condition and results of operations of Symphony GenIsis in its condensed consolidated financial statements. For a further discussion see Note 3 — *Strategic Alliances*.

As part of the collaboration between Isis and Ercole Biotech, Inc., during 2003 and early 2004, Isis paid Ercole $750,000 in exchange for a convertible promissory note. Isis expensed the payments when made. The promissory note will convert into securities that Ercole issues in a financing. Isis is not required to consolidate Ercole's results of operations under FIN 46R as Isis is not the primary beneficiary.

As part of the collaboration between Isis and Sarissa Inc., during February 2005, Isis licensed an anti-cancer antisense drug to Sarissa in exchange for a $1 million convertible promissory note. The promissory note will convert into securities that Sarissa issues in a financing. Isis has recognized a valuation allowance of $1 million to offset the debt instrument, as realization of this asset is uncertain. Isis is not required to consolidate Sarissa's results of operations under FIN 46R as Isis is not the primary beneficiary.

As part of the collaboration between Isis and iCo Therapeutics, Inc., during August 2005, Isis licensed iCo 007, an antisense drug, to iCo in exchange for a $500,000 upfront fee consisting of $250,000 in cash and a $250,000 convertible note. In December 2005, Isis entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo will purchase drug manufactured by Isis for $700,000. iCo made a $525,000 prepayment to Isis consisting of $175,000 in cash and a $350,000 convertible note. The remaining $175,000 will be paid upon shipment of the drug. Isis previously recognized a valuation allowance for both notes as realization of these assets was uncertain. In May 2006, Isis received 869,025 shares of iCo common stock for the conversion of both convertible notes. Isis is not required to consolidate iCo's results of operations under FIN 46R as Isis is not the primary beneficiary.

As part of the collaboration between Isis and Achaogen, Inc., during January 2006, Isis licensed its proprietary aminoglycosides program in exchange for $1.5 million of Achaogen Series A Preferred stock. Isis has recognized a valuation allowance of $1.5 million to offset the equity instrument, as realization of this asset is uncertain. Isis is not required to consolidate Achaogen's results of operations under FIN 46R as Isis is not the primary beneficiary.

Stock-Based Compensation

On January 1, 2006, Isis adopted SFAS 123R, *Share-Based Payment*, which requires the measurement and recognition of compensation expense for all stock-based payment awards made to employees and directors including employee stock options and employee stock purchases related to the Isis Employee Stock Purchase Plan ("ESPP") based on estimated fair values. SFAS 123R supersedes Isis' previous accounting under Accounting Principles Board Opinion No. 25, *Accounting for Stock Issued to Employees* ("APB 25") and SFAS 123, *Accounting for Stock-Based Compensation*, beginning January 1, 2006. In March 2005, the SEC issued SAB 107 relating to SFAS 123R. Isis has applied the provisions of SAB 107 in its adoption of SFAS 123R.

Isis adopted SFAS 123R using the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of the fiscal year 2006. Isis' Condensed Consolidated Statements of Operations as of and for the three and nine months ended September 30, 2006 reflects the impact of SFAS 123R. In accordance with the modified prospective transition method, Isis' Condensed Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact of SFAS 123R.

SFAS 123R requires companies to estimate the fair value of stock-based payment awards on the date of grant using an option-pricing model. The value of the portion of the award that is ultimately expected to vest is recognized as expense over the requisite service period as stock-based compensation expense in Isis' Condensed Consolidated Statements of Operations. For the three and nine months ended September 30, 2006, Isis' Condensed Consolidated Statements of Operations included compensation expense for stock-based payment awards granted prior to, but not yet vested as of December 31, 2005, based on the grant date fair value estimated in accordance with the pro forma provisions of SFAS 123 and compensation expense for the stock-based payment

awards granted subsequent to December 31, 2005 based on the grant date fair value estimated in accordance with the provisions of SFAS 123R. Isis recognizes compensation expense for all stock-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. As stock-based compensation expense recognized in the Condensed Statement of Operations for the first nine months of fiscal 2006 is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures. SFAS 123R requires forfeitures to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. In Isis' pro forma information required under SFAS 123 for the periods prior to fiscal 2006, Isis accounted for forfeitures as they occurred.

As permitted by SFAS 123R, Isis utilizes the Black-Scholes option-pricing model ("Black-Scholes model") as its method of valuation for stock-based awards granted. The Black-Scholes model was previously utilized for Isis' pro forma information required under SFAS 123. Isis' determination of the estimated fair value of stock-based payment awards on the date of grant using an option-pricing model is affected by Isis' stock price as well as assumptions regarding a number of

highly complex and subjective variables. These variables include, but are not limited to, Isis' expected stock price volatility over the term of the awards, and actual and projected employee stock option exercise behaviors. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because Isis' employee stock options have certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of Isis' employee stock options. Although the estimated fair value of employee stock options is determined in accordance with SFAS 123R using an option-pricing model, that value may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

Prior to January 1, 2006, Isis had adopted the disclosure-only provision of SFAS 123. Accordingly, Isis had not previously recognized compensation expense for the Isis stock option plans and Isis' ESPP, except for compensation expense primarily related to the affected options from the 2003 option exchange program. Non-cash stock-based compensation expense recognized under SFAS 123R for the three and nine months ended September 30, 2006 was $1.4 million and $4.2 million respectively. The non-cash stock-based compensation expense/(benefit) resulting from the 2003 option exchange program for the three and nine months ended September 30, 2005 was $15,000 and ($613,000), respectively.

In April 2003, Isis implemented an employee stock option exchange program that allowed employees during the offering period to surrender options granted prior to January 5, 2002. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1 million options having an exercise price of $5.15. The new options, fully vested as of January 31, 2006, expire on December 31, 2008. Isis previously accounted for the affected options using variable accounting consistent with the provisions of APB 25 and FIN 44. As a result, Isis recorded non-cash compensation expense/(benefit) related to stock options on the Condensed Consolidated Statements of Operations.

See Note 6—*Stockholders' Equity* for additional information regarding Isis' share-based compensation plans and the impact of adopting SFAS 123R.

Comprehensive Loss

SFAS 130, *Reporting Comprehensive Income*, requires Isis to report, in addition to net loss, comprehensive loss and its components. A summary follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Comprehensive loss:				
Change in unrealized gains (losses)	$ (60)	$ 2,515	$ (1,133)	$ 33
Income tax expense	—	(307)	—	(307)
Net loss applicable to common stock	(12,105)	(15,172)	(31,757)	(64,488)
Comprehensive loss	$ (12,165)	$ (12,964)	$ (32,890)	$ (64,762)

Included in comprehensive loss at September 30, 2005 was $307,000 of accrued income taxes on the conversion of the $100 million loan provided by Lilly.

Impact of Recently Issued Accounting Standards

In September 2006, the Financial Accounting Standards Board issued SFAS 157, *Fair Value Measurements.* This Statement defines fair value, establishes a framework for measuring fair value in generally accepted accounting principles and expands disclosures about fair value measurements. This statement applies across a broad number of other accounting pronouncements that require or permit fair value measurements. Accordingly, this Statement does not require any new fair value measurements, but the application of this Statement will change some current practices as they relate to the definition of fair value, the methods used to measure fair value and the expanded disclosure about fair value measurements. This Statement is effective for all financial statements issued for fiscal years that begin after November 15, 2007, and all interim periods for that year. Isis has not assessed the impact that adoption of SFAS 157 will have on its operating results and financial position.

3. Strategic Alliances

Drug Discovery and Development

Rosetta Genomics, Inc.

In January 2006, Isis initiated a joint research collaboration with Rosetta Genomics to discover and develop antisense drugs that regulate microRNAs for the treatment of the most prevalent type of liver cancer, hepatocellular carcinoma. For each drug that meets specific success factors outlined in the collaboration, Isis and Rosetta will mutually agree on a development strategy for the drug. This collaboration has an initial term of two years.

Achaogen, Inc.

In January 2006, Isis licensed its proprietary aminoglycosides program to Achaogen, a biotechnology company pursuing unique strategies to combat drug-resistant pathogens. Aminoglycosides are a group of antibiotics that inhibit bacterial protein synthesis and are used to treat serious bacterial infections. The program Isis licensed to Achaogen resulted from research conducted in Isis' Ibis Biosciences division to identify drugs to treat antibiotic-resistant infections in the early years of the division.

In exchange for the exclusive, worldwide license to Isis' aminoglycoside program, Achaogen issued to Isis $1.5 million of Achaogen Series A Preferred stock. In addition, assuming Achaogen successfully develops and commercializes the first drug in the first major market, Isis will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. In addition, Isis will receive royalties on sales of drugs resulting from the program. Achaogen is solely responsible for the continued development of the aminoglycoside program and products.

Symphony GenIsis, Inc.

On April 7, 2006, Isis entered into a series of related agreements in connection with a transaction with Symphony Capital and a group of co-investors to provide $75 million to fund the development of Isis' cholesterol-lowering drug, ISIS 301012, and two novel drugs from Isis' metabolic disease program. The financing will support ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing will also support development of the two novel diabetes drugs through initial proof of concept in human clinical trials. In addition to providing the financial support to move these drugs forward, the transaction allows Isis to continue to control and manage the development of these three drugs through key development milestones.

Symphony Capital formed Symphony GenIsis, capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with Isis. Isis licensed to Symphony GenIsis the intellectual property for its apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. Isis has received an exclusive purchase option from Symphony GenIsis' investors that will allow Isis to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price that reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. The purchase option exercise price may be paid in cash or a combination of cash and Isis common stock (up to 33% of the purchase price), at Isis' discretion.

In exchange for the purchase option, Isis granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share, a 25% premium over Isis' prior 60-day average trading price, which was $7.14. To compensate Symphony Capital for structuring the transaction and to pay a portion of its expenses, Isis paid a structuring fee of $3.75 million. Using a Black-Scholes option-pricing model, we estimated the fair value of the warrant, at the grant date, to be $18.6 million. Isis' determination of the fair value of the warrant on the date of grant using an option-pricing model is affected by Isis' stock price as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, Isis' expected stock price volatility over the term of the warrant. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because the warrant has certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of the warrant, specifically the value determined may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

In accordance with FIN 46R, Isis has determined that Symphony GenIsis is a variable interest entity for which it is the primary beneficiary. As a result, Isis includes the financial condition and results of operations of Symphony GenIsis in its condensed consolidated financial statements. Isis' condensed consolidated financial statements now include the cash and cash equivalents held by Symphony GenIsis. Additionally, the condensed consolidated financial statements include line items called "Noncontrolling interest in Symphony GenIsis." On the Condensed Consolidated Balance Sheets, this line item initially reflected the $75 million proceeds contributed into Symphony GenIsis less $4.1 million of structuring and legal fees and the $18.6 million fair value of the warrant issued by Isis to Symphony Capital. As Isis and Symphony GenIsis progress through their collaboration, this line item will be reduced by Symphony GenIsis' expenditures, which were $6.7 million and $20.3 million for the three and nine months ended September 30, 2006, respectively, until the balance becomes zero. The reductions to the "Noncontrolling Interest in Symphony GenIsis" will be reflected in Isis' Condensed Consolidated Statements of Operations using a similar caption and will improve Isis' reported net loss.

ImQuest Pharmaceuticals, Inc.

In April 2006, Isis granted an exclusive worldwide license to ImQuest for the development and commercialization of ISIS 5320, a compound that has been shown to be a potent and specific inhibitor of HIV, the virus that causes AIDS. ImQuest plans to develop ISIS 5320 as a topical microbicide therapy to prevent the sexual transmission of HIV throughout the world, but especially in developing countries. In exchange for the exclusive worldwide license, Isis will receive royalties on sales of drugs resulting from ISIS 5320. In addition, if ImQuest sublicenses ISIS 5320, Isis is entitled to a portion of the consideration received.

Ibis Biosciences Division

Bruker Daltonics, Inc.

In July 2006, Isis' Ibis Biosciences division entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker will be the exclusive, worldwide manufacturer of the Ibis T5000 Biosensor System and will also be responsible for order processing, system installations and service in North America, Europe and the Middle East. In Europe and the Middle East, Bruker will have exclusive rights to sell Ibis T5000 Biosensor Systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics.

4. Segment Information and Concentration of Business Risk

Segment Information

The following is information for revenue and loss from operations by segment (in thousands):

	Drug Discovery and Development	Ibis Biosciences	Corporate	Total
Three Months Ended September 30, 2006				
Revenue:				
Research and development	$ 330	$ 1,988	$ —	$ 2,318
Assay services (1)	—	151	—	151
Licensing and royalty	784	—	—	784
Total segment revenue	$ 1,114	$ 2,139	$ —	$ 3,253
Income (loss) from operations	$ (16,888)	$ (1,654)	$ 279	$ (18,264)
Three Months Ended September 30, 2005				
Revenue:				
Research and development	$ 3,693	$ 3,429	$ —	$ 7,122
Licensing and royalty	336	—	—	336
Total segment revenue	$ 4,029	$ 3,429	$ —	$ 7,458
Income (loss) from operations	$ (12,381)	$ (97)	$ (334)	$ (12,144)

	Drug Discovery and Development	Ibis Biosciences	Corporate	Total
Nine Months Ended September 30, 2006				
Revenue:				
Research and development	$ 3,513	$ 7,596	$ —	$ 11,109
Assay services (1)	—	151	—	151
Licensing and royalty	1,327	—	—	1,327
Total segment revenue	$ 4,840	$ 7,747	$ —	$ 12,587
Income (loss) from operations	$ (48,185)	$ (3,654)	$ 457	$ (51,382)
Nine Months Ended September 30, 2005				
Revenue:				
Research and development	$ 16,044	$ 8,651	$ —	$ 24,695
Licensing and royalty	797	—	—	797
Total segment revenue	$ 16,841	$ 8,651	$ —	$ 25,492
Income (loss) from operations	$ (40,199)	$ (1,603)	$ (6,772)	$ (48,574)

(1) Ibis Biosciences' assay services revenue has been classified as research and development revenue under collaborative agreements on Isis' Condensed Consolidated Statements of Operations.

Isis does not include asset or liability information by reportable segment since Isis does not currently segregate this information by segment and it is not used for purposes of making decisions about allocating resources to the segments and assessing their performance.

Concentrations of Business Risk

Isis does not generate sales from products but has historically funded its operations in part from collaborations with corporate partners and various government agencies. A relatively small number of partners historically have accounted for a significant percentage of Isis' revenue. Revenue from significant partners as a percentage of total revenue was as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Partner A	23%	11%	22%	10%
Partner B	23%	0%	6%	0%
Partner C	23%	6%	15%	4%
Partner D	4%	25%	15%	16%
Partner E	1%	26%	9%	43%
Partner F	0%	19%	4%	8%

For the three and nine months ended September 30, 2006, Isis derived approximately 66% and 62%, respectively, of its revenue from agencies of the United States Government, which includes approximately 35% and 24% of government derived revenue from two significant customers, respectively, for the nine months ended September 30, 2006.

Contract receivables from three significant partners comprised approximately 34%, 25% and 23% of contract receivables at September 30, 2006. Contract receivables from four significant partners comprised 39%, 13%, 12%, and 12% of contract receivables at December 31, 2005.

5. Restructuring Activities

In connection with the decision to refocus Isis' resources on key programs, in January 2005, Isis commenced several cost containment measures, including a reduction in workforce of approximately 160 employees, the consolidation of its facilities in the United States, and the closure of Isis' research and development laboratory in Singapore.

In the second quarter of 2006, Isis successfully negotiated a contract modification settlement with one of its vendors. The amount of the contract termination cost was $265,000 less than the amount that had been previously accrued; therefore Isis recognized a benefit for this amount in restructuring activities for the nine months ended September 30, 2006. Additionally, in the third quarter of 2006, Isis negotiated a lease termination agreement with the landlord of a building that Isis vacated in 2005 as part of the restructuring activities. The early termination of the lease resulted in a benefit of approximately $350,000 over what was previously accrued. This benefit is reflected in the restructuring activities for the three and nine months ended September 30, 2006.

Pursuant to SFAS 146, *Accounting for Costs Associated with Exit or Disposal Activities*, the following table sets forth the activity in the restructuring reserve, which is included in accrued liabilities at September 30, 2006 (in thousands).

	Facility Consolidation and Closure Related Costs	Contract Termination Costs	Other Costs	Total
Balance at December 31, 2005	$ 856	$ 765	$ 126	$ 1,747
Accrued and expensed	(295)	(265)	103	(457)
Charged against accrual	(485)	(500)	(117)	(1,102)
Balance at September 30, 2006	$ 76	$ —	$ 112	$ 188

6. Stockholders' Equity

Common Stock

In May 2006, after receiving approval from its stockholders, Isis amended its Restated Certificate of Incorporation to increase the authorized number of shares of its common stock from 100,000,000 shares to 200,000,000 shares.

Azimuth Opportunity Ltd.

On May 30, 2006, Isis entered into an equity line of credit arrangement with Azimuth Opportunity Ltd. Specifically, Isis entered into a Common Stock Purchase Agreement with Azimuth, which provides that, upon the terms and subject to the conditions set forth therein, Azimuth is committed to purchase up to $75.0 million of Isis' common stock, or 14,578,970 shares whichever occurs first, over the 18-month term of the purchase agreement. From time to time over the term of the purchase agreement, and at Isis' sole discretion, Isis may present Azimuth with draw down notices constituting offers to purchase Isis' common stock. The per share purchase price for these shares is at a discount ranging from 3.8% to 5.3%.

To date, Isis has made two draw downs under the Azimuth equity line totaling $20.0 million. In July 2006, Isis completed its first draw down of $5.0 million by issuing 872,330 shares at a weighted average price of $5.73 per share. In October 2006, Isis completed its second draw down of $15.0 million by issuing 1,835,213 shares at a weighted average price of $8.17 per share. After completing these first two draws, $55 million, or 11,871,427 shares, whichever occurs first, remains available under the equity line.

Stock Option Plans

1989 Stock Option Plan and Other Employee Option Grants

The 1989 Stock Option Plan (the "1989 Plan") provides for the issuance of non-qualified and incentive stock options for the purchase of up to 13,200,000 shares of common stock to its employees, directors, and consultants. The term of the plan is scheduled to end in January 2014. Options granted after December 31, 1995 vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vested over a five-year period. Options granted after May 26, 2004 have a term of seven years while options granted before May 26, 2004 have a term of ten years. As of September 30, 2006, 2,464,478 shares were available for future grant.

2000 Broad-Based Equity Incentive Plan

The 2000 Broad-Based Equity Incentive Plan (the "2000 Plan") provides for the issuance of non-qualified stock options for the purchase of up to 5,990,000 shares of common stock to its employees, directors, and consultants. Typically options expire ten years from the date of grant. Options granted under this plan generally vest over a four-year period, with 25% exercisable at the end of one year from the date of the grant and the balance vesting ratably thereafter. Options granted under this plan pursuant to the April 2003 stock option exchange program expire on December 31, 2008 and vested 33.34% on January 1, 2004 and then at the rate of 2.78% per month during the option holder's employment. Options were fully vested on January 31, 2006. As of September 30, 2006, 2,177,194 shares were available for future grant.

2002 Non-Employee Directors' Stock Option Plan

In September 2001, Isis' Board of Directors adopted, and the stockholders subsequently approved, an amendment and restatement of the 1992 Non-Employee Directors' Stock Option Plan, which provides for the issuance of non-qualified stock options to Isis' non-employee directors. The name of the resulting new plan is the 2002 Non-Employee Directors' Stock Option Plan (the "2002 Plan"). In May 2006, after receiving approval from its stockholders, Isis amended its 2002 Plan to increase the total number of shares reserved for issuance under the 2002 Plan from 600,000 shares to 850,000 shares. Options under this plan expire ten years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. As of September 30, 2006, 374,000 shares were available for future grant.

Employee Stock Purchase Plan

Under the 2000 ESPP, Isis reserved 200,000 shares of common stock for issuance. In each of the subsequent years, an additional 200,000 shares of common stock were reserved for the ESPP, resulting in a total of 1.4 million shares authorized in the plan. The plan permits full-time employees to purchase common stock through payroll deductions (which cannot exceed 10% of each employee's compensation) at the lower of 85% of fair market value at the beginning of the offering period or the end of each six-month purchase period. At September 30, 2006, 100,054 shares were available for purchase under this plan.

Stock Option Activity and Stock-Based Compensation Expense

The following table summarizes stock option activity for the nine months ended September 30, 2006 (in thousands, except per share and contractual life data):

	Number of Shares	Weighted Average Price Per Share	Average Remaining Contractual Term (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2005	7,979	$ 7.86		
Granted	2,185	$ 5.71		
Exercised	(583)	$ 5.84		
Cancelled/forfeited/ expired	(721)	$ 8.24		
Outstanding at September 30, 2006	8,860	$ 7.43	5.13	$ 10,692
Exercisable at September 30, 2006	5,506	$ 8.44	4.40	$ 4,628

The following table summarizes information concerning outstanding and exercisable options as of September 30, 2006 (in thousands, except contractual life and exercise price data):

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number Outstanding	Weighted Average Remaining Contractual Life	Weighted Average Exercise Price	Number Exercisable	Weighted Average Exercise Price
$2.86 - $5.24	1,060	4.43	$ 4.82	721	$ 4.91
$5.25 - $5.72	1,500	6.31	$ 5.28	78	$ 5.54
$5.76 - $6.59	1,596	5.76	$ 5.95	684	$ 6.01
$6.60 - $6.81	1,456	5.27	$ 6.81	1,208	$ 6.81
$6.813 - $9.25	1,509	5.48	$ 7.32	1,077	$ 7.23
$9.38 - $22.83	1,739	3.56	$ 12.88	1,738	$ 12.88
	8,860	5.13	$ 7.43	5,506	$ 8.44

The weighted-average estimated fair values of options granted were $4.11 and $3.35 for the three and nine months ended September 30, 2006, respectively, compared to $2.50 and $3.64 for the same periods in 2005. The total intrinsic value of options exercised during the three and nine months ended September 30, 2006 was $209,000 and $4.7 million, respectively, which was determined as of the date of exercise. The amount of cash received from the exercise of stock options was $170,000 and $3.4 million for the three and nine months ended September 30, 2006, respectively. As of September 30, 2006, there was $7.5 million of total unrecognized compensation cost related to non-vested stock-based compensation plans. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.35 years.

Stock-based Valuation and Compensation Expense Information under SFAS 123R

Impact of the Adoption of SFAS 123R

The following table summarizes stock-based compensation expense related to employee stock options and employee stock purchases under SFAS 123R for the three and nine months ended September 30, 2006 (in thousands, except per share data), which was allocated as follows:

	Three Months Ended September 30, 2006	Nine Months Ended September 30, 2006
Research and development	$ 1,091	$ 3,348
Selling, general and administrative	326	842
Non-cash compensation expense related to stock options included in operating expenses	$ 1,417	$ 4,190
Basic and diluted net loss per share	$ 0.02	$ 0.06

Prior to the adoption of SFAS 123R, Isis had adopted the disclosure-only provision of SFAS 123. Accordingly, Isis had not previously recognized compensation expense for the Isis stock option plans and the ESPP, except for compensation expense primarily related to the affected options from the 2003 option exchange program.

Prior to the adoption of SFAS 123R, Isis presented deferred compensation as a separate component of stockholders' equity. In accordance with the provisions of SFAS 123R, on January 1, 2006, Isis reclassified the balance in deferred compensation to additional paid-in capital on the balance sheet.

The table below reflects net loss along with basic and diluted net loss per share (in thousands, except per share amounts) assuming Isis determined compensation expense consistent with SFAS 123 for the three and nine months ended September 30, 2005:

	Three Months Ended September 30, 2005	Nine Months Ended September 30, 2005
Net loss applicable to common stock – as reported	$ (15,172)	$ (64,488)
Net loss applicable to common stock – pro forma	$ (16,494)	$ (68,787)
Basic and diluted net loss per share – as reported	$ (0.24)	$ (1.08)
Basic and diluted net loss per share – pro forma	$ (0.26)	$ (1.15)

Determining Fair Value

Valuation. Isis utilizes the Black-Scholes model as its method of valuation for stock-based awards granted. Isis recognizes the value of the portion of the award that is ultimately expected to vest as expense over the requisite service period as stock-based compensation expense in Isis' Condensed Consolidated Statements of Operations. Isis recognizes compensation expense for all stock-based payment awards using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period.

Isis estimated the fair value of each stock option grant and the ESPP purchase rights on the date of grant using the Black-Scholes model with the following weighted-average assumptions (annualized percentages), which vary based on type of plan, for the nine months ended September 30, 2006:

Employee Stock Option Plans:

	September 30, 2006	September 30, 2005
Risk-free interest rate	4.9%	4.1%
Dividend yield	0.0%	0.0%
Volatility	68.7%	81.5%
Expected Life	4.6 years	4.8 years

2002 Plan:

	September 30, 2006	September 30, 2005
Risk-free interest rate	5.2%	4.1%
Dividend yield	0.0%	0.0%
Volatility	85.2%	81.5%
Expected Life	7.0 years	4.8 years

Employee Stock Purchase Plan:

	September 30, 2006	September 30, 2005
Risk-free interest rate	5.31%	3.38%
Dividend yield	0.0%	0.0%
Volatility	55.5%	46.1%
Expected Life	6 months	6 months

Risk-Free Interest Rate. The risk-free interest rate assumption is based upon observed interest rates appropriate for the term of Isis' stock option plans or ESPP.

Dividend Yield. The dividend yield assumption is based on Isis' history and expectation of dividend payouts. Isis has not paid dividends in the past and does not expect to in the future.

Volatility. Isis used a weighted average of the historical stock price volatility of Isis' stock for the Black-Scholes model consistent with SFAS 123R. Prior to fiscal 2006, Isis also used its historical stock price volatility in accordance with SFAS 123 for purposes of its pro forma information.

Expected Life. The expected term of stock options granted represents the period of time that they are expected to be outstanding. For the 2002 Plan, Isis estimated the expected term of options granted based on historical exercise patterns. For the employee stock option plans, the estimated expected term is a derived output of the simplified method, as allowed under SAB 107.

Forfeitures. As stock-based compensation expense recognized in the Condensed Consolidated Statements of Operations is based on awards ultimately expected to vest, it has been reduced for estimated forfeitures. SFAS 123R requires forfeitures to be estimated at the time of grant and revised, if

necessary, in subsequent periods if actual forfeitures differ from those estimates. Forfeitures were estimated based on historical experience. In Isis' pro forma information required under SFAS 123 for the periods prior to fiscal 2006, Isis accounted for forfeitures as they occurred.

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

In addition to historical information contained in this Report on Form 10-Q, this Report contains forward-looking statements regarding our business, the financial position of Isis Pharmaceuticals, Inc. and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing systems to identify infectious organisms that are effective and commercially attractive, and in the endeavor of building a business around such products. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2005, 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 34 of this Report.

Overview

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We have designed antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding the capabilities of antisense drugs in treating disease. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and successfully turned our expertise into one marketed product and currently 14 drugs, which we continue to advance in preclinical and clinical development either internally or with our partners. Most of these are in Phase 1 and Phase 2 human clinical trials. Our internal drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Our partners are focused in disease areas such as inflammatory, ocular, viral, neurodegenerative diseases and cancer. We are expanding the therapeutic opportunities for antisense drugs by developing a variety of formulations to enhance patient convenience and compliance, as well as infrequent dose administration. Our pipeline has matured to consist primarily of drugs based on our proprietary second generation chemistry. Our second generation antisense drugs offer a number of advantages over first generation drugs. Specifically, second generation drugs offer the potential for improved safety and increased potency. In addition, because second generation drugs have a longer half-life, they have the potential to produce a durable therapeutic response and to support more convenient, less frequent dosing.

To date, we and our partners have made important progress on all of our second generation drugs in development. In particular, we reported positive results from Phase 1, Phase 2 and animal studies of ISIS 301012, our apoB-100 inhibitor for the lowering of high cholesterol. In a Phase 1 study, ISIS 301012 produced rapid, dose-dependent and prolonged reductions in apoB-100, low-density lipoprotein cholesterol, or LDL, and very low-density lipoprotein, or VLDL, total cholesterol and triglycerides, and was well tolerated. These positive results supported the initiation of a Phase 2 development program for ISIS 301012. In a Phase 2 study of ISIS 301012 as a single-agent in patients with high cholesterol, ISIS 301012 continued to produce rapid, dose-dependent and prolonged reductions in apoB-100, LDL, VLDL, total cholesterol and triglycerides. At a dose of 200 mg/week for three months, ISIS 301012 achieved a median percent reduction from baseline of 47% in apoB-100, 42% in LDL, 34% in total cholesterol and 46% in triglycerides at day 99. ISIS 301012 was well tolerated in this study. Additionally, in a drug-drug interaction study, ISIS 301012 did not interact with simvastatin or ezetimibe, currently available lipid lowering drugs with which ISIS 301012 may be dosed in combination. In addition, the U.S. Food and Drug Administration has granted orphan drug status to ISIS 301012 for the treatment of patients with homozygous familial hypercholesterolemia. The Phase 2 development program for ISIS 301012 is progressing in multiple studies and the drug continues to exhibit strong safety and efficacy profiles.

For ISIS 113715, our PTP-1b inhibitor for the treatment of type 2 diabetes, we reported data from a Phase 2 study in diabetic patients in which ISIS 113715 improved glucose control, did not cause hypoglycemia and was well tolerated. We also recently announced the initiation of a study to examine ISIS 113715 in combination with other antidiabetic drugs. Our partnered drugs in development also met important milestones. For example, in the first quarter of 2006, OncoGenex Technologies, Inc. announced encouraging data from a Phase 1 study of OGX-011 in patients with non-small cell lung cancer, which supports their ongoing Phase 2 study. Phase 2 studies evaluating OGX-011 in prostrate and breast cancers are

also ongoing. Earlier this year, Eli Lilly and Company initiated Phase 1 studies of LY2275796, a cancer drug targeting eIF-4E and the second drug from our research collaboration.

We have a broad patent portfolio covering our technologies. We own or exclusively license approximately 1,500 issued patents, which we believe represents the largest antisense and RNA-oriented patent estate in the pharmaceutical industry. Our intellectual property is a strategic asset that we are exploiting to generate near-term revenue and that we expect will also provide us with revenue in the future. As of September 30, 2006, we had generated more than $76 million from our intellectual property licensing program that helps support our internal drug discovery and development programs. In October 2006, we received an $8.0 million payment from Drug Royalty USA, Inc. as partial payment for the monetization of Isis' royalty rights in Macugen.

In our Ibis Biosciences division, we have developed a revolutionary biosensor system that can, with a single test, simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample. Our Ibis scientists have advanced application development through contracts with our government partners in the areas of biodefense, epidemiological surveillance, biological products screening and forensics. This work is important to us in that we can also apply much of this application development to commercial opportunities. Ibis' recent achievements represent important steps in implementing its commercial plan.

Through our Ibis Biosciences division, we plan to commercialize the Ibis T5000 Biosensor System and related assay kits. The commercial applications for the Ibis T5000 Biosensor System include biodefense, human forensics, epidemiolgy, infectious disease surveillance, hospital-acquired

infection control and *in vitro* diagnostics. To date we have delivered four systems to our government partners for use in biodefense and epidemiological surveillance. Ibis recently received its first commercial order for two Ibis T5000 Biosensor Systems from a U.S. government agency for human forensics applications. Ibis plans to install the first system under this order before the end of the year and the second system early in 2007. In addition, in the third quarter of 2006, Ibis Biosciences began earning commercial revenue from analyzing samples in its Assay Services Laboratory. In addition to being a revenue generating opportunity for Ibis Biosciences, the Assay Services Laboratory provides customers with the ability to evaluate the capabilities of the Ibis T5000 Biosensor System before making a buying decision.

Consistent with Ibis' commercialization strategy, in July 2006, we entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker will be the exclusive, worldwide manufacturer of the Ibis T5000 Biosensor System and will also be responsible for order processing, system installations and service in North America, Europe and the Middle East. In Europe and the Middle East, Bruker will have exclusive rights to sell Ibis T5000 Biosensor Systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics.

Much of the development of the Ibis T5000 system and related applications has been funded through government contracts and grants. As of September 30, 2006, we had earned $55.6 million in revenue since inception from numerous government agencies including the Department of Homeland Security (DHS), the Centers for Disease Control (CDC), the National Institute of Allergy and Infectious Diseases (the NIAID), a part of the National Institutes of Health (NIH), and others. In addition, we have an additional $8.0 million committed under our existing contracts and grants.

We pursue early-stage antisense research programs, including RNA interference (RNAi), microRNA, and alternative splicing through research collaborations and partnerships, similar to our strategic alliances with Alnylam Pharmaceuticals, Inc. (Alnylam), Rosetta and Ercole. In the third quarter of 2006, we earned licensing revenue of $750,000 from Alnylam as a result of Alnylam's recently announced alliance with a major pharmaceutical company for the development of RNAi therapeutics.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development. We continue to utilize our proprietary technology to discover and characterize novel antisense inhibitors through which our scientists modify the properties of our antisense drugs for optimal use with particular targets and thus, produce a broad proprietary portfolio of compounds applicable to many disease targets. Further, our scientists have made significant advances in oligonucleotide chemistries, including what we call our second generation antisense drugs. Second generation, including generation 2.2, drugs provide increased potency, stability, oral bioavailability and an improved side effect profile. We and our partners are studying antisense drugs in intravenous, subcutaneous, intravitreal, enema, aerosol, intrathecal, oral and topical formulations.

Along with our partners, we currently have 14 drugs in development, of which five are in Phase 2 clinical development, two are in Phase 1 clinical development and seven are in preclinical development. Our partners are licensed to develop, with our support, eight of these 14 drugs, which substantially reduces our development costs.

Ibis Biosciences Division. Our Ibis Biosciences division has developed the Ibis T5000 Biosensor System for rapid identification and characterization of infectious agents. The Ibis T5000 is capable of identifying virtually all bacteria, virus and fungi, and can provide information about drug resistance, virulence and strain type of these pathogens. Ibis Biosciences plans to commercialize the Ibis T5000 Biosensor System and related assay kits. The commercial applications for the Ibis T5000 Biosensor System include biodefense, human forensics, epidemiolgy, infectious disease surveillance, hospital-acquired infection control and *in vitro* diagnostics.

Recent Events

Symphony GenIsis, Inc.

In April 2006, we entered into a series of related agreements in connection with a transaction with Symphony Capital and a group of co-investors to provide $75 million to fund the development of our cholesterol-lowering drug, ISIS 301012, and two novel drugs from our metabolic disease program. The financing supports ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and the completion of Phase 2b clinical trials in patients with high cholesterol. The financing also supports development of the two novel diabetes drugs through initial proof of concept in human clinical trials. In addition to providing the financial support to move these drugs forward aggressively, the transaction allows us to continue to control and manage the development of these three drugs through key development milestones.

Symphony Capital formed Symphony GenIsis, Inc., capitalized with $75 million, to provide funding for the development of these three drugs in collaboration with us. We licensed to Symphony GenIsis the intellectual property for our apoB-100, glucagon receptor (GCGR) and glucocorticoid receptor (GCCR) programs. We have received an exclusive purchase option from Symphony GenIsis' investors that will allow us to reacquire the intellectual property by purchasing all of Symphony GenIsis' equity at a predetermined price that reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. The purchase option exercise price may be paid in cash or a combination of cash and our common stock (up to 33% of the purchase price), at our discretion.

In exchange for the purchase option, we granted to Symphony GenIsis Holdings LLC a five-year warrant to purchase 4.25 million shares of common stock at an exercise price of $8.93 per share, a 25% premium over our prior 60-day average trading price, which was $7.14. To compensate Symphony Capital for structuring the transaction and to pay a portion of its expenses, we paid a structuring fee of $3.75 million. Using a Black-Scholes option-pricing model, the fair value of the warrant, at the grant date, was estimated to be $18.6 million. Our determination of the fair value of the warrant on the date of grant using an option-pricing model is affected by our stock price as well as assumptions regarding a number of highly complex and subjective variables. These variables include, but are not limited to, our expected stock price volatility over the term of the warrant. Option-pricing models were developed for use in estimating the value of traded options that have no vesting or hedging restrictions and are fully transferable. Because the warrant has certain characteristics that are significantly different from traded options, and because changes in the subjective assumptions can materially affect the estimated value, in management's opinion, the existing valuation models may not provide an accurate measure of the fair value of the warrant,

specifically the value determined may not be indicative of the fair value observed in a willing buyer/willing seller market transaction.

In accordance with FIN 46R, we have determined that Symphony GenIsis is a variable interest entity for which we are the primary beneficiary. As a result, we include the financial condition and results of operations of Symphony GenIsis in our condensed consolidated financial statements. Our condensed consolidated financial statements include the cash and cash equivalents held by Symphony GenIsis. Additionally, the condensed consolidated financial statements include line items called "Noncontrolling interest in Symphony GenIsis." On the Condensed Consolidated Balance Sheets, this line item initially reflected the $75 million proceeds contributed into Symphony GenIsis less $4.1 million of structuring and legal fees and the $18.6 million fair value of the warrant issued by us to Symphony Capital. As we and Symphony GenIsis progress through our collaboration, this line item will be reduced by Symphony GenIsis' expenditures, which were $6.7 million and $20.3 million in the three and nine months ended September 30, 2006, respectively, until the balance becomes zero. The reductions to the "Noncontrolling Interest in Symphony GenIsis" will be reflected in our Condensed Consolidated Statements of Operations using a similar caption and will improve our reported net loss.

Consistent with our expectations, the $6.7 million recognized as a benefit in the Noncontrolling Interest in Symphony GenIsis in the third quarter of 2006 was lower than the $13.6 million that was recognized in the second quarter of 2006. In the second quarter of 2006, the amount recognized in the Noncontrolling Interest in Symphony GenIsis included various one-time items that will not occur again during the last half of 2006. In the fourth quarter of 2006, we anticipate the Noncontrolling Interest in Symphony GenIsis to slightly increase from the amount recognized in the third quarter. In 2007, as the development of the compounds under the Symphony collaboration continue to progress, we anticipate Symphony GenIsis' expenditures to increase, and therefore the benefit to our net loss applicable to common stock to increase accordingly.

Azimuth Opportunity Ltd.

On May 30, 2006, we entered into an equity line of credit arrangement with Azimuth Opportunity Ltd. Specifically, we entered into a Common Stock Purchase Agreement with Azimuth, which provides that, upon the terms and subject to the conditions set forth therein, Azimuth is committed to purchase up to $75 million of our common stock, or 14,578,970 shares whichever occurs first, over the 18-month term of the purchase agreement. From time to time over the term of the purchase agreement, and at our sole discretion, we may present Azimuth with draw down notices constituting offers to purchase our common stock. The per share purchase price for these shares is at a discount ranging from 3.8% to 5.3%. To date, we have drawn down $20 million under the Azimuth equity line by issuing 2,707,543 shares at a weighted average price of approximately $7.39 per share. For the third quarter ended September 30, 2006, our Condensed Consolidated Balance Sheet reflected 872,330 shares issued for the $5 million initial draw at a weighted average price of approximately $5.73 per share.

Critical Accounting Policies

We prepare our condensed consolidated financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These judgments involve making estimates about the effect of matters that are inherently uncertain and may significantly impact our quarterly or annual results of operations and financial condition. We discuss the development, selection and disclosure of such estimates with our audit committee each quarter. There are specific risks associated with these critical accounting policies that we describe in the following paragraphs. For all of these policies, we caution that future events rarely develop exactly as expected, and that best estimates routinely require adjustment. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, require the following:

- Assessment of the propriety of revenue recognition and associated deferred revenue;
- Determination of the proper valuation of investments in marketable securities and other equity investments;
- Estimations to assess the recoverability of long-lived assets, including property and equipment, intellectual property and licensed technology;
- Determination of the proper valuation of inventory;

- Determination of the appropriate cost estimates for unbilled preclinical studies and clinical development activities;
- Estimation of our net deferred income tax asset valuation allowance;
- Determination of the appropriateness of the judgments and estimates used in allocating revenue and expenses to operating segments; and
- Estimations to determine the fair value of stock-based compensation, which includes the expected life of the option, the expected stock price volatility over the term of the expected life and estimated forfeitures.

Descriptions of these critical accounting policies follow.

Revenue Recognition

We follow the provisions set forth by current accounting rules, which primarily include SAB 101, *Revenue Recognition in Financial Statements*, SAB 104, *Revenue Recognition*, and EITF 00-21, *Accounting for Revenue Arrangements with Multiple Deliverables*.

We generally recognize revenue when we have satisfied all contractual obligations and we are reasonably assured of collecting the resulting receivable. We are often entitled to bill our customers and receive payment from our customers in advance of recognizing the revenue under current

accounting rules. In those instances where we have billed our customers or received payment from our customers in advance of recognizing revenue, we include the amounts in deferred revenue on the balance sheet.

We often enter into collaborations where we receive non-refundable up-front payments for prior or future expenditures. We recognize revenue related to up-front payments ratably over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligations when the agreements we enter into do not clearly define such information. Should different estimates prevail, revenue recognized could be materially different. We have made estimates of our continuing obligations on several agreements, including our collaborations with Antisense Therapeutics Ltd. ("ATL"), Lilly, OncoGenex, and Pfizer.

As part of our Lilly alliance, in 2001 Lilly provided us a $100 million interest-free loan to fund the companies' joint research collaboration. We took quarterly draw downs against this loan and discounted the amounts to their net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We accreted the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan represented value Lilly gave to us to help fund the research collaboration. We accounted for this difference as deferred revenue and recognized it as revenue over the period of contractual performance. In August 2005, in accordance with its terms, we converted this loan into 2.5 million shares of our common stock. Concurrent with the conversion, we extended the research collaboration. As part of the conversion and collaboration extension, Lilly has agreed not to sell these shares until at least the fourth quarter of 2006, assuming the collaboration is not terminated earlier, in exchange for certain credits against milestones and royalties in the event of a stock price decline.

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

We often enter into agreements to license our proprietary patent rights on an exclusive or non-exclusive basis in exchange for license and/or royalty fees. We generally recognize as revenue immediately those licensing and royalty fees for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable. In the third quarter of 2006, we earned licensing revenue of $750,000 from Alnylam as a result of Alnylam's recently announced alliance with a major pharmaceutical company for the development of RNAi therapeutics. In addition, in October 2006, we received an $8 million payment from Drug Royalty USA, Inc. as partial payment for the monetization of Isis' royalty rights in Macugen.

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

Valuation of Investments in Marketable Securities

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

In addition to our investments in marketable securities, we also have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is other-than-temporary, we examine historical trends in the stock price, the financial condition of the issuer, near-term prospects of the issuer, and our current need for cash. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During the second quarter of 2006, we recorded a net gain on investments. This net gain on investments represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we own offset by a non-cash loss on investment of $465,000 related to the impairment of our equity investment in ATL, which we believe is primarily a result of current financial market conditions related to biotechnology companies.

Valuation of Long-Lived Assets

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

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

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

In the first nine months of 2006 and 2005, we incurred charges of $2.2 million and $14.8 million, respectively, related to the write-down of tangible and intangible assets, including equipment and patent costs that were non-essential to our current focus. The charge in 2005 was primarily related to our restructuring activities, which were primarily related to the sale of three of our buildings.

Valuation of Inventory

We include in inventory raw material costs for drugs that we manufacture for our partners under contractual terms

and that we use primarily in our clinical development activities and drug products. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value of our inventory, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. Total inventory, which consisted solely of raw materials, was $632,000 and $951,000 as of September 30, 2006 and December 31, 2005, respectively.

Estimated Liability for Clinical Development Costs

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

Valuation Allowance for Net Deferred Tax Assets

We recorded a valuation allowance to offset our net deferred tax assets because we are uncertain that we will realize these net tax assets. When and if circumstances warrant, we will assess the likelihood that our net deferred tax assets will more likely than not be recovered from future taxable income and record an appropriate reversal to the valuation allowance. Because we have had net operating losses since inception, we have established a 100% valuation allowance for our net deferred tax asset.

Segment Information

We provide segment financial information and results for our Drug Discovery and Development segment and our Ibis Biosciences division based on the segregation of revenue and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment.

Stock-Based Compensation

Prior to January 1, 2006, we adopted the disclosure-only provision of SFAS 123, *Accounting for Stock-Based Compensation*. Accordingly, we have not previously recognized compensation expense for our stock option plans and our ESPP, except for compensation expense primarily related to the variable accounting of options from the 2003 option exchange program.

Effective January 1, 2006, we adopted SFAS 123R, *Share-Based Payment*, which requires the measurement and recognition of compensation expense for all stock-based payment awards made to employees and directors including employee stock options and employee stock purchases related to our ESPP based on estimated fair values. We elected to use the modified prospective transition method, which requires the application of the accounting standard as of January 1, 2006, the first day of our fiscal year 2006. Our Condensed Consolidated Statements of Operations as of and for the three and nine months ended September 30, 2006 reflect the impact of SFAS 123R. In accordance with the modified prospective transition method, our Condensed Consolidated Statements of Operations for prior periods have not been restated to reflect, and do not include, the impact of SFAS 123R. As of September 30, 2006, there was $7.5 million of total unrecognized compensation cost related to non-vested stock-based compensation plans. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. We expect to recognize that cost over a weighted average period of 1.35 years.

We utilize the Black-Scholes model and assumptions discussed in Note 6 for estimating the fair value of the stock-based awards we granted. Compensation expense for all stock-based payment awards will continue to be recognized using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting

method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. Our risk-free interest rate assumption is based upon observed interest rates appropriate for the term of our employee stock options and our ESPP. The dividend yield assumption is based on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use a weighted average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model consistent with SFAS 123R. The expected term of stock options granted represents the period of time that they are expected to be outstanding. For the 2002 Non-Employee Directors' Stock Option Plan, we estimate the expected term of options granted based on historical exercise patterns. For the employee stock option plans, the estimated expected term

is a derived output of the simplified method, as allowed under SAB 107. We estimated forfeitures based on historical experience. For the periods prior to fiscal 2006, we accounted for forfeitures as they occurred in our pro forma information as required under SFAS 123.

Results of Operations

Revenue

Total revenue for the three and nine months ended September 30, 2006 was $3.3 million and $12.6 million, respectively, compared to $7.5 million and $25.5 million for the same periods in 2005. Our ability to maintain revenue at current levels will depend on new revenue sources and the expansion of existing revenue sources for the remainder of 2006.

The following table sets forth information on our revenue by segment (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Drug Discovery and Development:				
Research and development revenue	$ 330	$ 3,693	$ 3,513	$ 16,044
Licensing and royalty revenue	784	336	1,327	797
	$ 1,114	$ 4,029	$ 4,840	$ 16,841
Ibis Biosciences Division				
Research and development revenue	$ 1,988	$ 3,429	$ 7,596	$ 8,651
Assay services revenue (1)	151	—	151	—
Licensing and royalty revenue	—	—	—	—
	$ 2,139	$ 3,429	$ 7,747	$ 8,651
Total Revenue:				
Research and development revenue	$ 2,318	$ 7,122	$ 11,109	$ 24,695
Assay services revenue (1)	151	—	151	—
Licensing and royalty revenue	784	336	1,327	797
	$ 3,253	$ 7,458	$ 12,587	$ 25,492

(1) Ibis Biosciences' assay services revenue has been classified as research and development revenue under collaborative agreements on Isis' Condensed Consolidated Statements of Operations.

Drug Discovery and Development

Revenue for our drug discovery and development segment includes revenue from research and development under collaborative agreements and licensing and royalty revenue. Research and development revenue under collaborative agreements for the three and nine months ended September 30, 2006 was $330,000 and $3.5 million, respectively, compared to $3.7 million and $16.0 million for the same periods in 2005. The decrease for the three and nine months ended September 30, 2006 compared to the same periods in 2005 was primarily due to a decrease in revenue associated with our collaboration with Lilly, which was extended in August 2005 to focus on a select number of targets. Our revenue fluctuates based on the timing of activities under contract, and as a result, it frequently includes non-recurring items. For example, in 2005, we earned revenue from milestones we achieved under our collaboration with Pfizer. Our revenue from licensing activities and royalties for the three and nine months ended September 30, 2006 was $784,000 and $1.3 million, respectively, compared to

$336,000 and $797,000 for the same periods in 2005. The increase for the three and nine months ended September 30, 2006 compared to the same periods in 2005, was primarily related to revenue we earned in the third quarter of 2006 from Alnylam as a result of Alnylam's recently announced alliance with a major pharmaceutical company for the development of RNA interference (RNAi) therapeutics.

Ibis Biosciences Division

To develop the Ibis T5000 Biosensor System and related assay kits, our Ibis Biosciences division receives contracts and grants from U.S. government agencies. To date, Ibis has delivered four systems to our government partners for use in biodefense and epidemiological surveillance. Ibis recently received its first commercial order for two Ibis T5000 Biosensor Systems from a U.S. government agency for human forensics applications. Ibis plans to install the first system under this order before the end of the year and the second system early in 2007. In addition, in the third quarter of 2006, Ibis began earning commercial revenue from analyzing samples in its Assay Services Laboratory. Ibis' recent achievements represent important steps in implementing its commercial plan.

In the third quarter of 2006, Ibis earned $151,000 of commercial revenue from analyzing samples in its Assay Services Laboratory. In addition, Ibis generated revenue from government contracts and grants of $2.0 million and $7.6 million for the three and nine months ended September 30, 2006, respectively, compared to revenue of $3.4 million and $8.7 million for the same periods in 2005. Ibis' revenue from government contracts fluctuates based on when the contracts are awarded, the period of performance for the contracts and the funding amount of the contracts. For example, in 2006, two large government contracts that were active in 2005 ended, resulting in reduced revenue in the first nine months of 2006 compared to the same period in 2005 offset by several new contracts. Additionally, Ibis recently announced that it has successfully completed the first phase of its Challenge Grant from the NIAID, a part of the NIH, and has been granted funding for subsequent phases that provide for the installation of an Ibis T5000 Biosensor System at Johns Hopkins University Medical Center. Ibis expects that this additional funding, combined with extensions of other existing contracts and new contracts will be the basis for Ibis' revenue from government contracts in the fourth quarter of 2006 and in 2007.

We receive our DARPA funding through a subcontract with San Diego-based Science Applications International Corporation or SAIC. Historically, we have generated the majority of our government-funded revenue through our collaboration with SAIC. This collaboration accounted for approximately 15% and 16% of our total revenue in the first nine months of 2006 and 2005, respectively, which represents 24% and 48% of our 2006 and 2005 Ibis Biosciences revenue, respectively. In the future, we expect that the percentage of revenue from SAIC will decrease as we continue to obtain additional contracts from other government agencies.

From inception through September 30, 2006, Ibis Biosciences has earned $55.6 million in revenue from various government agencies to further the development of our Ibis T5000 Biosensor System and related assay kits. An additional $8.0 million is committed under existing contracts and grants. We may receive additional funding under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of contract options by the contracting agencies. These agencies may terminate these contracts and grants at their convenience at any time, even if we have fully performed our obligations. Consequently, we may never receive the full amount of the potential value of these awards.

Operating Expenses

Total operating expenses for the three and nine months ended September 30, 2006 were $21.5 million and $64.0 million, respectively, compared to $19.6 million and $74.1 million for the same periods in 2005. We achieved a 14% decrease in our operating expenses in the first nine months of 2006 compared to the same period in 2005. The decrease in operating expenses for the nine months ended September 30, 2006 compared to the same period in 2005 reflected the impact of our reorganization in the first quarter of 2005. As anticipated, our operating expenses for the third quarter rose slightly in comparison to the average operating expenses for the first half of 2006. We expect operating expenses to continue to increase slightly during the fourth quarter of 2006 as we continue to expand the ISIS 301012 development program.

Included in our operating results for the three and nine months ended September 30, 2006 was $1.4 million and $4.2 million, respectively, of non-cash compensation expense related to stock options as required by SFAS 123R. Our operating expenses for the three and nine months ended September 30, 2005 included non-cash compensation expense/(benefit) of $15,000 and ($613,000), respectively, as a result of variable accounting for stock options. In order to analyze and compare our results of operations to other similar companies, we believe that it is important to exclude non-cash compensation related

to stock options and costs associated with restructuring activities, which are not part of ongoing operations. We believe these items are not indicative of our operating results or cash flows from our operations. Further, we internally evaluate the performance of our operations excluding these items.

Our research and development expenses consist of costs for antisense drug discovery, antisense drug development, manufacturing and operations, our Ibis Biosciences division and R&D support costs. The following table sets forth information on research and development costs (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Research and development expenses	$ 17,882	$ 18,212	$ 52,979	$ 61,523
Non-cash compensation expense related to stock options	1,091	—	3,348	—
Total research and development as reported	$ 18,973	$ 18,212	$ 56,327	$ 61,523

Our research and development expenses by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Drug Discovery and Development	$ 15,915	$ 14,919	$ 46,715	$ 52,051
Ibis Biosciences Division	3,058	3,293	9,612	9,472
Total research and development expenses	$ 18,973	$ 18,212	$ 56,327	$ 61,523

For the three and nine months ended September 30, 2006, we incurred total research and development expenses, excluding stock compensation, of $17.9 million and $53.0 million, respectively, compared to $18.2 million and $61.5 million for the same periods in 2005. The $8.5 million decrease in the first nine months of 2006 compared to the same period in 2005, is attributed to cost savings achieved as a result of our restructuring activities, including significant reductions in personnel costs. We anticipate operating expenses to increase slightly in the fourth quarter of 2006 as we continue to advance the expansion of the ISIS 301012 program.

Antisense Drug Discovery

Antisense drug discovery costs for the three and nine months ended September 30, 2006 were $3.2 million and $9.9 million, respectively, compared to $3.8 million and $13.8 million for the same periods in 2005. The decrease of $3.9 million for the first nine months of 2006 compared to the same period in 2005 was principally the result of a decrease in personnel costs resulting from our 2005 restructuring activities. We anticipate that our existing relationships and collaborations, as well as prospective new partners, will continue to help fund our research programs, as well as contribute to the advancement of the science by funding core antisense technology research.

Antisense Drug Development

The following table sets forth research and development expenses for our major antisense drug development projects (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Alicaforsen for Crohn's disease	$ 3	$ 60	$ 5	$ 403
Other antisense development products	2,951	3,699	10,425	14,388
Development overhead costs	2,592	1,370	7,389	5,059
Total antisense drug development	$ 5,546	$ 5,129	$ 17,819	$ 19,850

Antisense drug development expenditures were $5.5 million and $17.8 million for the three and nine months ended September 30, 2006, respectively, compared to $5.1 million and $19.9 million for the same periods in 2005. The decrease of $2.1 million for the first nine months of 2006 compared to the same period in 2005 was primarily due to cost savings resulting from our decision to focus our research and development resources on our key programs, specifically ISIS 301012 and ISIS 113715, and the decision to discontinue development of ISIS 104838, ISIS 14803 and alicaforsen for Crohn's disease. These reductions were offset by increased spending on ISIS 301012 in the third quarter of 2006 compared to the same period in 2005. The increased spending on ISIS 301012 is a result of the expansion of the development program for this drug. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials. We may conduct multiple clinical trials on a drug candidate, including multiple clinical trials for the various indications we may be studying. Furthermore, as we obtain results from trials we may elect to discontinue clinical trials for certain drug candidates in certain indications in order to focus our resources on more promising drug candidates or indications. Our Phase 1 and Phase 2 programs are really research programs that fuel our Phase 3 pipeline. When our products are in Phase 1 or Phase 2 clinical trials, they are in a dynamic state where we continually adjust the development strategy for each product. Although we may characterize a product as "in Phase 1" or "in Phase 2," it does not mean that we are conducting a single, well-defined study with dedicated resources. Instead, we allocate our internal resources on a shared basis across numerous products based on each product's particular needs at that time. This means we are constantly shifting resources among products. Therefore, what we spend on each product during a particular period is usually a function of what is required to keep the products progressing in clinical development, not what products we think are most important. For example, the number of people required to start a new study is large, the number of people required to keep a study going is modest and the number of people required to finish a study is large. However, such fluctuations are not indicative of a shift in our emphasis from one product to another and cannot be used to accurately predict future costs for each product. And, because we always have numerous products in preclinical and early stage clinical research, the fluctuations in expenses from product to product, in large part, offset one another. If we partner a drug, it may affect the size of a trial, its timing, its total cost and the timing of the related cost. Our partners are developing, with our support, eight of our 14 drug candidates, which substantially reduces our development costs.

Manufacturing and Operations

Expenditures in our manufacturing and operations function consist primarily of personnel costs, specialized chemicals for oligonucleotide manufacturing, laboratory supplies and outside services. This function is responsible for providing drug supplies to antisense research and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements. These costs for the three and nine months ended September 30, 2006 were $1.4 million and $4.4 million, respectively, compared to $1.6 million and $4.9 million for the same periods in 2005. The decrease for the three and nine months ended September 30, 2006 was primarily related to decreased personnel costs resulting from our 2005 restructuring activities. Also contributing to the decrease was lower levels of oligonucleotide manufacturing in 2006 compared to 2005.

Ibis Biosciences Division

Our Ibis research and development expenses are primarily the result of our performance under our government contracts in support of our ongoing development of our Ibis T5000 Biosensor System and related assay kits. Our Ibis expenses include all contract-related costs we incur on behalf of government agencies in connection with the performance of our obligations under the respective contracts, including costs for equipment to which the government retains title. Research and development expenditures in Ibis Biosciences include costs for scientists, pass-through equipment costs, laboratory

supplies, chemicals and highly specialized information technology consultants to advance the research and development of our Ibis T5000 Biosensor System. In 2006, Ibis is incurring costs to support deployed Ibis biosensor systems and the preparations necessary to move towards commercialization. Further, we allocate a portion of R&D support costs and selling, general and administrative costs to Ibis. Ibis' research and development expenses, excluding stock-based compensation, for the three and nine months ended September 30, 2006, were $2.9 million and $9.1 million, respectively, compared to $3.3 million and $9.5 million for the same periods in 2005. The decrease primarily reflects a decrease in pass-through equipment costs under our government contracts in the three and nine months ended September 30, 2006 compared to the same periods in 2005. Ibis has delivered four systems to its government partners for use in biodefense and epidemiological surveillance. Ibis recently received its first commercial order for two Ibis T5000 Biosensor Systems from a U.S. government agency for human forensics applications. In addition, in the third quarter of 2006, Ibis Biosciences began earning commercial revenue from analyzing samples in its Assay Services Laboratory. We expect costs and expenses for our Ibis Biosciences division to increase as we continue to expand this business.

R&D Support

In our research and development expenses, we include support costs such as rent, repair and maintenance for buildings and equipment, utilities, depreciation of laboratory equipment and facilities, amortization of our intellectual property, information technology costs, procurement costs and waste disposal costs. We call these costs R&D support costs.

The following table sets forth information on R&D support costs (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Personnel costs	$ 1,405	$ 1,447	$ 4,403	$ 4,330
Occupancy	1,553	1,600	4,480	5,318
Depreciation and amortization	2,692	1,312	5,267	3,854
Insurance	255	278	775	872
Other	323	467	1,207	1,253
Total R&D support costs	$ 6,228	$ 5,104	$ 16,132	$ 15,627

R&D support costs for the three and nine months ended September 30, 2006 were $6.2 million and $16.1 million, respectively, compared to $5.1 million and $15.6 million for the same periods in 2005. The increase of $505,000 in the first nine months of 2006 compared to the same period in 2005 was primarily due to an increase in patent application costs that were abandoned and written-off during the nine months ended September 30, 2006 compared to the same period in 2005 offset by decreased facilities expenses resulting from our restructuring activities, which included consolidation and closure of facilities and the write-down of equipment.

Our R&D support costs by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Drug Discovery and Development	$ 5,659	$ 4,333	$ 14,276	$ 13,456
Ibis Biosciences Division	569	771	1,856	2,171
Total R&D support costs	$ 6,228	$ 5,104	$ 16,132	$ 15,627

Selling, General and Administrative

The following table sets forth information on selling, general and administrative expenses (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Selling, general and administrative expenses	$ 2,497	$ 1,724	$ 7,257	$ 5,771
Non-cash compensation expense related to stock options	326	—	842	—
Total selling, general and administrative as reported	$ 2,823	$ 1,724	$ 8,099	$ 5,771

Selling, general and administrative expenses, excluding stock-based compensation expense, for the three and nine months ended September 30, 2006 were $2.5 million and $7.3 million, respectively, compared to $1.7 million and $5.8 million for the same periods in 2005. The increase for the three and nine months ended September 30, 2006 compared to the same periods in 2005 is a result of increased selling, general and administrative expenses associated with the commercialization of the Ibis T5000 Biosensor System, the addition of general and administrative expenses that are consolidated from Symphony GenIsis and legal fees incurred for the Ajinomoto arbitration. As Ibis continues to execute its commercialization plan, we expect selling, general and administrative expense for Ibis to continue to increase.

Our selling, general and administrative expenses by segment were as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2006	2005	2006	2005
Drug Discovery and Development	$ 2,087	$ 1,491	$ 6,310	$ 4,988
Ibis Biosciences Division	736	233	1,789	783
Total selling, general and administrative expenses	$ 2,823	$ 1,724	$ 8,099	$ 5,771

Compensation Expense Related to the Variable Accounting of Stock Options

Compensation expense/(benefit) related to the variable accounting of stock options for the three and nine months ended September 30, 2005 was $15,000 and ($613,000), respectively. Changes in compensation expense/(benefit) were primarily related to the effects of using variable accounting to account for stock options associated with the employee stock option exchange program initiated in April 2003. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with APB 25 and FIN 44.

Restructuring Activities

During the three and nine months ended September 30, 2006, we recorded a benefit of $279,000 and $457,000, respectively, compared to ($349,000) and $7.4 million of (benefit)/expense for the same periods in 2005 for restructuring activities resulting from our decision to focus our resources on key programs. The 2005 charge for restructuring activities consisted of costs associated with employee terminations, the consolidation of our facilities, termination of certain contractual obligations, and the closure of our research and development laboratory in Singapore.

In the second quarter of 2006, we successfully negotiated a contract modification with one of our vendors. The amount of the contract modification was $265,000 less than the amount that had been previously accrued; therefore, we recognized a benefit for this amount in restructuring activities for the nine months ended September 30, 2006. Additionally in the third quarter of 2006, we negotiated a lease termination agreement with the landlord of a building that we vacated in 2005 as part of the restructuring activities. The early termination of the lease resulted in a benefit of approximately $350,000 over what was previously accrued. This benefit is reflected in the restructuring activities for the three and nine months ended September 30, 2006.

Investment Income

Investment income for the three and nine months ended September 30, 2006 totaled $1.7 million and $3.8 million, respectively, compared to $1.2 million and $2.1 million for the same periods in 2005. The increase in investment income for the three and nine months ended September 30, 2006 compared to the same periods in 2005 was primarily due to our higher

average returns on our investments caused by higher interest rates for the first nine months of 2006 compared to the first nine months of 2005 and a higher average cash balance as a result of the funds held by Symphony GenIsis.

Interest Expense

Interest expense for the three and nine months ended September 30, 2006 totaled $2.3 million and $6.8 million, respectively, compared to $4.3 million and $18.0 million for the same periods in 2005. This decrease was due to the effect of a lower debt balance during 2006 than during 2005 primarily related to the conversion of our $100 million Lilly loan in the third quarter of 2005.

Gain on Investments, net

Gain on investments for the three and nine months ended September 30, 2006 was $0 and $2.3 million, respectively and $0 for the same periods in 2005. The gain on investments in 2006 reflected a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we own offset by a non-cash loss of $465,000 related to the impairment of our equity investment in ATL. The impairment reflects the decrease in the market value of ATL's stock, which we believe is a result of current financial market conditions related to biotechnology companies.

Net Loss Applicable to Common Stock

Net loss applicable to common stock for the three and nine months ended September 30, 2006 was $12.1 million and $31.8 million, respectively, compared with a net loss applicable to common stock of $15.2 million and $64.5 million, for the same periods in 2005. As a result of consolidating the results of Symphony GenIsis, we recognized a benefit of $6.7 million and $20.3 million, respectively in the Noncontrolling Interest in Symphony GenIsis for the three and nine months ended September 30, 2006. This benefit was a significant reason for the improvement in our net loss applicable to common stock in the first nine months of 2006 compared to the same period in 2005. The decrease in the net loss applicable to common stock was also impacted by an increase from the gain on investments and a decrease in interest expense offset by an increase in our loss from operations.

Consistent with our expectations, the $6.7 million recognized as a benefit in the Noncontrolling Interest in Symphony GenIsis in the third quarter of 2006 was lower than the $13.6 million that was recognized in the second quarter of 2006. In the second quarter of 2006, the amount recognized in the Noncontrolling Interest in Symphony GenIsis included various one-time items that will not occur again during the last half of 2006. In the fourth quarter of 2006, we anticipate the Noncontrolling Interest in Symphony GenIsis to slightly increase from the amount recognized in the third quarter. In 2007, as the development of the compounds under the Symphony collaboration continue to progress, we anticipate Symphony GenIsis' expenditures to increase, and therefore the benefit to our net loss applicable to common stock to increase accordingly.

Net Loss Per Share

Net loss per share for the three and nine months ended September 30, 2006 was $0.16 and $0.44 per share, respectively, compared to a net loss per share for the same periods in 2005 of $0.24 and $1.08 per share. In August 2005, we issued approximately 12 million shares of common stock in a private placement that raised net proceeds of $48 million. Also in August 2005, we issued 2.5 million shares to Lilly in connection with the conversion of our $100 million Lilly loan. These additional shares combined with the substantial decrease in net loss applicable to common stock, were a significant reason for the decrease in net loss per share for the first nine months of 2006 compared to the same period in 2005. As we make additional draw downs on our equity line with Azimuth, we expect further dilution.

Liquidity and Capital Resources

We have financed our operations with revenue from research and development under collaborative agreements and from affiliates. Additionally, we have earned licensing and royalty revenue from the sale or licensing of our intellectual property. We have also financed our operations through the sale of our equity securities and the issuance of long-term debt. From our inception through September 30, 2006, we have earned approximately $495.8 million in revenue from contract research and development and the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $651.4 million from the sale of equity securities. We have borrowed approximately $386.7 million under long-term debt arrangements to finance a portion of our operations.

At September 30, 2006, we had cash, cash equivalents and short-term investments of $126.9 million, which includes $58.6 million of cash and cash equivalents held by Symphony GenIsis. We had consolidated working capital of $117.5 million and stockholders' equity of $1.6 million. In comparison, we had cash, cash equivalents and short-term investments of $94.4 million, working capital of $82.1 million and stockholders' equity of $2.7 million as of December 31, 2005. The increase in our cash, cash equivalents and short-term investments and working capital were due primarily to the consolidation of the cash and cash equivalents held by Symphony GenIsis along with proceeds of $5.0 million that we received from the initial draw down under the Azimuth equity financing, $4.4 million that we received from the sale of a portion of our Alnylam equity securities and amounts received from contracts and stock option exercises, offset by cash used in operations.

As of September 30, 2006, our debt and other obligations totaled $142.4 million, compared to $147.8 million at December 31, 2005. We will continue to use lease financing as long as the terms are commercially attractive.

Based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the end of 2008. The following table summarizes our contractual obligations as of September 30, 2006. The table provides a breakdown of when obligations become due. A more detailed description of the major components of our debt is provided in the paragraphs following the table:

	Payments Due by Period (in millions)				
Contractual Obligations (selected balances described below)	**Total**	**Less than 1 year**	**1-3 years**	**3-5 years**	**After 5 years**
5 1/2% Convertible Subordinated Notes	$ 125.0	$ —	$ 125.0	$ —	$ —
Silicon Valley Bank Term Loan	15.6	6.6	9.0	—	—
Capital Lease and Other Obligations	1.8	1.1	0.5	0.1	0.1
Operating Leases	23.5	3.0	5.5	4.4	10.6

Our contractual obligations consist primarily of our publicly traded convertible debt. In addition, we also have a term loan from Silicon Valley Bank, capital leases and other obligations.

In December 2003, we secured a $32 million term loan from Silicon Valley Bank to retire our existing debt to Boehringer Ingelheim, and Elan Corporation. We amortize the term loan over sixty months. The term loan requires equal monthly payments of principal plus accrued interest, and bears interest at the prime interest rate less applicable discounts based on the balances in the cash and investment accounts that we maintain at Silicon Valley Bank, which was 8% at September 30, 2006. The loan is secured by substantially all of our operating assets, excluding intellectual property, real estate and certain equity investments. The loan is subject to certain liquidity requirements, including a requirement that we maintain a minimum balance in an account at Silicon Valley Bank at all times equal to the outstanding balance of the loan. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. The carrying value of the term loan at September 30, 2006 was $15.6 million.

In May 2002, we completed a $125 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. The subordinated notes bear interest at 5.5%, which is payable semi-annually, and mature in May 2009. Holders of the subordinated notes can, at any time, convert the notes into shares of common stock at a conversion price of $16.625 per share. At September 30, 2006, the principal outstanding on the notes was $125 million.

In addition to contractual obligations, we had outstanding purchase orders as of September 30, 2006 for the purchase of services, equipment and materials as part of our normal course of business.

In May 2006, we obtained a $75 million equity financing commitment from Azimuth Opportunity Ltd. Under this arrangement, we may at our discretion, from time to time, sell registered shares of our common stock at a small discount, ranging from 3.8% to 5.3%, to the market price to Azimuth Opportunity over the 18-month term of the purchase agreement. To date, we have drawn down $20 million under the Azimuth equity line by issuing 2,707,543 shares at a weighted average price of approximately $7.39 per share, which leaves $55 million, or 11,871,427 shares, whichever occurs first, still available under the equity line. For the third quarter ended September 30, 2006, our Condensed Consolidated Balance Sheet reflected 872,330 shares issued for the $5 million initial draw at a weighted average price of approximately $5.73 per share.

We plan to continue to enter into more collaborations with partners to provide for additional revenue and cash to us, and we may be required to incur additional cash expenditures related to our obligations under any of the new agreements we may enter into. We currently intend to use our cash and short-term equivalents to finance our activities. However, we

may also pursue other financing alternatives, like issuing additional shares of our common stock, issuing debt instruments, refinancing our existing debt or securing lines of credit. Whether we use our existing capital resources or choose to obtain financing will depend on various factors, including the future success of our business, the prevailing interest rate environment and the condition of financial markets generally.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this report on Form 10-Q, you should carefully consider the risks described below before purchasing our securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment. We have marked with an asterisk those risk factors that reflect substantive changes from the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2005.

Risks Associated with our Businesses as a Whole

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

Because product discovery and development require substantial lead-time and money prior to commercialization, our expenses have exceeded our revenue since we were founded in January 1989. As of September 30, 2006, we had accumulated losses of approximately $802.6 million and stockholders' equity of approximately $1.6 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from selling, general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

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

All of our product candidates are 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 reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated requirements through at least the end of 2008. If we do not meet our goals to commercialize our products, or to license our drugs and proprietary technologies, we will need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements;
- continued scientific progress in our research, drug discovery and development programs;
- the size of our programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in developing and commercializing a business based on our Ibis T5000 Biosensor System to identify infectious organisms; and

- the profile and launch timing of our drugs.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If we raise additional funds by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available or not available on acceptable terms, we may have to cut back on one or more of our research, drug discovery or development programs. For example, in January 2005 we decided to terminate the development of two lower priority drugs, ISIS 14803 and ISIS 104838. Alternatively, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies, product candidates or products.

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

To date, 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.

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

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

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may suffer. These collaborations may not continue or result in commercialized drugs. Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. For example, in November 2004 based on the outcome of both Phase 3 trials, Lilly discontinued its investment in Affinitak.

Other drugs in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, iCo Therapeutics, Inc., ImQuest Pharmaceuticals, Inc., OncoGenex Technologies Inc. and Lilly. We have received significant financial support from United States Government-funded grants and contracts for our Ibis Biosciences division and the development of our Ibis T5000 Biosensor System. The United States Government can unilaterally terminate these contracts and grants at its convenience at any time, even if we have fully performed our obligations. If any of these pharmaceutical companies or government partners stopped funding and/or developing these products, our business could suffer and we may not have the resources available to develop these products on our own.

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

In addition, the disappointing results of the two Affinitak trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn’s disease, or any future clinical trial failures could impair our ability to attract new collaborative partners. If we cannot continue to secure additional collaborative partners, our revenues could decrease and the development of our drugs could suffer.

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

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

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

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

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we may have to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to needed 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, like when a certain product candidate will enter the clinic, when we will complete a clinical trial, or when we will file an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If we do not achieve milestones when we expect to, investors could be disappointed and the price of our securities would likely decrease.

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

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our executive officers. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of our securities. During the 12 months preceding September 30, 2006, the market price of our common stock ranged from $4.20 to $9.50 per share. Many factors can affect the market price of our securities, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new 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.

If a natural or man-made disaster strikes our research and development facilities, it could delay our progress developing and commercializing our drugs or our Ibis T5000 Biosensor System.

We are developing our Ibis T5000 Biosensor System in our facility located in Carlsbad, California. Additionally, we manufacture our research and clinical supplies in a separate manufacturing facility located in Carlsbad, California. The facilities and the equipment we use to develop the Ibis T5000 Biosensor System and manufacture our drugs would be costly to replace and could require substantial lead time to repair or replace. Either of our facilities may be harmed by natural or man-made disasters, including, without limitation, earthquakes, floods and fires, and in the event they are affected by a disaster, our development and commercialization efforts would be delayed. Although we possess insurance for damage to our property and the disruption of our business from casualties, this insurance may not be sufficient to cover all of our potential losses and may not continue to be available to us on acceptable terms, or at all.

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

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

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

If registration rights that we have previously granted are exercised or shares under our shelf registration statement are issued, then the price of our securities may be negatively affected.*

We have granted registration rights to Lilly and Symphony GenIsis Holdings LLC, which cover approximately 6.75 million shares of our common stock, which we issued to Lilly upon the conversion of outstanding convertible securities or are issuable upon the exercise of the warrant we issued to Symphony GenIsis Holdings. We also registered for resale 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of the warrant, which we issued as part of our August 2005 private placement. In addition, on December 22, 2005, we filed a Form S-3 shelf registration statement with the SEC to register up to $200,000,000 worth of our common stock for possible issuance. The addition of these shares into the market may have an adverse effect on the price of our securities.

If we sell shares of our common stock under our equity line of credit arrangement, our existing common stockholders will experience immediate dilution and our stock price may fall.*

We have entered into a common stock purchase agreement with Azimuth Opportunity Ltd., which provides that, upon the terms and subject to the conditions set forth therein, Azimuth is committed to purchase up to $75 million of our common stock, or 14,578,970 shares, whichever occurs first over the 18-month term of the purchase agreement. From time to time over the term of the purchase agreement, and at our sole discretion, we may present Azimuth with draw down notices constituting offers to purchase our common stock. The per share purchase price for these shares is at a discount ranging from 3.8% to 5.3%. As a result, our existing common stockholders will experience immediate dilution upon the purchase of any shares of our common stock by Azimuth.

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

Each year we are required to evaluate our internal controls systems in order to allow management to report on and our Independent Registered Public Accounting Firm to attest to, our internal controls as required by Section 404 of the Sarbanes-Oxley Act. As a result, we will incur additional expenses and will suffer a diversion of management's time. In addition, if we cannot continue to comply with the requirements of Section 404 in a timely manner, we might be subject to sanctions or investigation by regulatory authorities, such as the Securities and Exchange Commission, the Public Company Accounting Oversight Board (PCAOB) or the NASDAQ Stock Exchange. Any such action could adversely affect our financial results and the market price of our common stock.

Risks Associated with our Drug Discovery and Development Business

If we or our partners fail to obtain regulatory approval for our drug candidates, 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 drugs before a drug can be approved for sale. We must conduct these trials in compliance with United States 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 drugs, 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. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drugs. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug, we and our partners must comply with comprehensive government

regulations regarding how we manufacture, market and distribute drug products. If we fail to comply with these regulations, regulators could force us to withdraw a drug from the market or impose other penalties or requirements that also could have a negative impact on our financial results.

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

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 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; the risk that a compound is not safe or effective for use in humans; and the risk that successful results in early human clinical trials may not be indicative of results in late-stage clinical trials. Antisense technology in particular is relatively new and unproven. We are applying most of our resources to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drugs that have not met the primary clinical end points in their Phase 3 studies.

In March 2003, we reported the results of a Phase 3 clinical trial of Affinitak in patients with late-stage non-small cell lung cancer and in October 2004, we reported the results of a second similar Phase 3 clinical trial. In each case, Affinitak failed to demonstrate improved survival sufficient enough to support an NDA filing. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, in which alicaforsen did not demonstrate statistically significant induction of clinical remissions compared to placebo. Similar results could occur with the trials for our other drugs. If any of our drugs in clinical studies do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization goals for this and other drugs and our stock price could decline.

We have licensed the intellectual property, including commercialization rights, to our apoB-100, GCGR, and GCCR programs to Symphony GenIsis, Inc. and will not receive any future royalties or revenues with respect to the products in these programs, including ISIS 301012 and ISIS 325568 unless we exercise our option to acquire all of these product candidates in the future. We may not have the financial resources to exercise this option or sufficient clinical data in order to determine whether we should exercise this option.*

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our apoB-100, GCGR, and GCCR Programs in exchange for Symphony GenIsis' investment of $75 million to advance the clinical development of these programs. In exchange for this investment and for the five-year warrant to purchase shares of our common stock, we received an exclusive purchase option to acquire all of the equity of Symphony GenIsis, thereby allowing us to reacquire our apoB-100, GCGR and GCCR programs, which include ISIS 301012 and ISIS 325568. The purchase option exercise price reflects a compounded annual rate of return that averages 32% and is 27% at the end of the anticipated four-year collaborative development period. We may pay the option exercise price in cash or a combination of cash and our common stock, at our sole discretion, provided that the common stock portion may not exceed 33% of the purchase option exercise price.

If we elect to exercise the repurchase option, we will be required to make a substantial cash payment and/or issue a substantial number of shares of our common stock, or enter into a financing arrangement or license arrangement with one or more third parties, or some combination of the foregoing. A payment in cash would substantially reduce our capital resources. A payment in shares of our common stock will result in dilution to our stockholders at that time. Other financing or licensing alternatives may be expensive or impossible to obtain. If we do not exercise the purchase options prior to their expiration, we will lose our rights in our apoB-100, GCGR, and GCCR programs. We may not have the financial resources to exercise the repurchase option, which would result in our loss of these rights. Additionally, we may not have sufficient clinical data in order to determine whether we should exercise the options.

Disagreements between Symphony GenIsis and us regarding the development of our product candidates in our apoB-100, GCGR, and GCCR programs may cause significant delays and other impediments in the development of these product candidates, which could negatively affect the

value of these product candidates.*

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our product candidates in our apoB-100, GCGR, and GCCR programs in exchange for Symphony GenIsis' investment of $75 million to advance the clinical development of these programs. We are responsible for developing these product candidates in accordance with a specified development plan and related development budget. The Symphony GenIsis development committee supervises our development activities. The development committee is comprised of an equal number of representatives from Isis and Symphony GenIsis. If the development committee cannot resolve a particular development issue, the issue will be referred to the chief executive officers of Isis and Symphony GenIsis. Any disagreements between Symphony GenIsis and us regarding a development decision may cause significant delays in the development and commercialization of our product candidates within our apoB-100, GCGR, and GCCR programs.

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

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

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

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

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

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

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

If our drug discovery and development business fails to compete effectively, our drugs 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 drugs or technologies that are more effective than any drugs or technologies that we are developing. These competitive developments could make our products obsolete or non-competitive.

Many of our competitors have substantially greater financial, technical and human resources than we do. In addition, many of these competitors have significantly greater experience than we do in conducting preclinical testing and human clinical trials of new pharmaceutical products and in obtaining FDA and other regulatory approvals of products for use in health care. Accordingly, our competitors may succeed in obtaining regulatory approval for products earlier than we do. We will also compete with respect to marketing and sales capabilities, areas in which we have limited or no experience.

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

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

Risks Associated with our Ibis Biosciences Division

We may not successfully develop or derive revenues from our business based on our Ibis T5000 Biosensor System.

Our Ibis T5000 Biosensor System is subject to the risks inherent in developing tools based on innovative technologies. Our product is at an early stage of development and requires additional research and development prior to marketing. If our potential customers fail to purchase our Ibis T5000 Biosensor System due to competition or other factors, or if we fail to develop applications that lead to market acceptance, we could lose our investment in this technology and our Ibis T5000 Biosensor System business could fail to meet our business and financial objectives.

We will depend on Bruker Daltonics to manufacture the Ibis T5000 Biosensor System and any failure of Bruker to fulfill its obligations could harm or delay our commercialization efforts.*

In July 2006, Ibis Biosciences entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker will be the exclusive, worldwide manufacturer of the Ibis T5000 Biosensor System and will also be responsible for order processing, system installations and service in North America, Europe and the Middle East. In Europe and the Middle East, Bruker will have exclusive rights to sell Ibis T5000 Biosensor Systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. As such, we rely heavily on Bruker to successfully manufacture and distribute our Ibis T5000 Biosensor System, but do not control many aspects of Bruker's activities. If Bruker fails to carry out its obligations under our alliance, such failure could harm or delay the commercialization of our Ibis T5000 Biosensor System.

If we fail to secure additional commercial partners for our Ibis T5000 Biosensor System, our commercialization efforts for our Ibis T5000 Biosensor System may be harmed or delayed.*

In addition to Bruker, we may depend on third parties to commercialize our Ibis T5000 Biosensor System, particularly in the areas of hospital-associated infection control and infectious disease diagnostics. If we are unable to reach agreements with suitable third parties, we may fail to meet our business objectives for the Ibis T5000 Biosensor System. We may not successfully establish a relationship in these markets or be able to make alternative arrangements. Moreover, these relationships may not succeed, may require us to give up a part of our ownership interest, or may diminish our revenue targets on our Ibis Biosciences instruments and related assay kits.

We depend on government contracts for most of our revenues and the loss of government contracts or a decline in funding of existing or future government contracts could adversely affect our revenues and cash flows and our ability to fund our growth.*

Virtually all of our Ibis Biosciences business' revenue is from the sale of services and products to the United States government. The U.S. government may cancel these contracts at any time without penalty or may change its requirements, programs or contract budget or decline to exercise option periods, any of which could reduce our revenues and cash flows from U.S. government contracts. Our revenues and cash flow from U.S. government contracts could also be reduced by declines in U.S. defense, homeland security and other federal agency budgets.

For the nine months ended September 30, 2006, we derived approximately 62% of our revenue from agencies of the United States government, including through our subcontract with SAIC. Because of the concentration of our contracts, we are vulnerable to adverse changes in our revenues and cash flows if a significant number of our United States Government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons. If United States defense and other federal agencies choose to reduce their purchases under our contracts, exercise their right to terminate contracts, fail to exercise options to renew contracts or limit our ability to obtain new contract awards, our revenues and cash flows could be adversely affected.

We may be liable for penalties under a variety of procurement rules and regulations, and changes in government regulations could adversely impact our revenues, operating expenses and operating margins.

Under our agreements with the United States government, we must comply with and are affected by various government regulations that impact our operating costs, operating margins and our internal organization and operation of our businesses. These regulations affect how our customers and we do business and, in some instances, impose added costs on our businesses. Any changes in applicable laws could adversely affect the financial performance of our Ibis Biosciences business. With respect to U.S. government contracts, any failure to comply with applicable laws could result in contract termination, price or fee reductions or suspension or debarment from contracting with the U.S. government. Among the most significant regulations are the following:

- the U.S. Federal Acquisition Regulations, which comprehensively regulate the formation, administration and performance of government contracts;
- the U.S. Truth in Negotiations Act, which requires certification and disclosure of all cost and pricing data in connection with contract negotiations; and
- the U.S. Cost Accounting Standards, which impose accounting requirements that govern our right to reimbursement under certain cost-based government contracts.

If our Ibis T5000 Biosensor System's reliability does not meet market expectations, we may be unable to retain our existing customers and attract new customers.

Complex instruments such as our Ibis T5000 Biosensor System typically require operating and reliability improvements following their initial introduction. As we continue to develop our Ibis T5000 Biosensor System and its related applications we will need to make sure our customers are satisfied with the sensor's reliability. Our efforts to satisfy our customer's needs for instrument reliability could result in greater than anticipated service expenses or divert other resources. Additionally, if we fail to resolve reliability issues as they develop, we could materially damage our reputation, which could prevent us from retaining our existing customers and attracting new customers.

If we had to replace a supplier of one of the major hardware components of our Ibis T5000 Biosensor System, it could delay our commercialization efforts and lengthen our sales cycle.

We have a single supplier for each major hardware component of our Ibis T5000 Biosensor System. Although, we believe we would be able to find a replacement provider, if any of these suppliers stopped providing us with their respective components, identifying and securing a suitable replacement could delay our commercialization efforts and lengthen our sales cycle.

If our Ibis Biosciences business fails to compete effectively, it may not succeed or contribute significant revenues.

Many of our competitors have, and in the future these and other competitors may have, significantly greater

financial, marketing, sales, manufacturing, distribution and technological resources than us. Moreover, these companies may have substantially greater expertise in conducting clinical trials and research and development, greater ability to obtain necessary intellectual property licenses and greater brand recognition than we do. In addition, our competitors may be in a better position to respond quickly to new or emerging technologies, may be able to undertake more extensive marketing campaigns, may adopt more aggressive pricing policies and may be more successful in attracting potential customers, employees and strategic partners than we are.

The diagnostics industry is highly competitive. Currently, large reference laboratories, public health laboratories and hospitals perform the majority of diagnostic tests used by physicians and other health care providers. We expect that these laboratories will compete vigorously to maintain their dominance in the diagnostic testing market. In order to achieve market acceptance of our Ibis T5000 Biosensor System, we will be required to demonstrate that it provides accurate, cost-effective and/or time saving alternatives to tests performed by traditional laboratory procedures and products made by our competitors.

Improvements in preventing major diseases could reduce the need for our Ibis T5000 Biosensor instruments and related assay kits, which in turn could reduce our revenues.

We expect to derive a significant portion of our revenues from the sale of assay kits necessary to use our Ibis T5000 Biosensor System. The need to quickly identify and contain major threats, such as the avian flu, could increase the demand for our assay kits. Conversely, improvements in containing or treating a threat, such as vaccines, would significantly reduce the need to identify and contain the threat. Any reduction in the need to identify or contain a threat could diminish the need for our assay kits, which could reduce our revenues.

Our plans to commercialize the Ibis T5000 internationally are subject to additional risks that could negatively affect our operating results.*

Our success will depend in part on our ability to market and sell Ibis T5000 biosensors and assay kits in foreign markets. Expanding our international operations could impose substantial burdens on our resources, divert management's attention from domestic operations and otherwise adversely affect our business. Furthermore, international operations are subject to several inherent risks including:

- Trade protective measures and import or export licensing requirements or other restrictive actions by U.S. and foreign governments could prevent or limit our international sales;
- Reduced protection of intellectual property rights;
- Changes in foreign currency exchange rates;
- Changes in specific country's or region's political or economic conditions; and
- Changes in tax laws.

If we cannot access or license rights to particular nucleic acid sequences for targeted diseases in the future, we may be limited in our ability to develop new products and access new markets.

Although our research staff seeks to discover particular nucleic acid sequences for targeted diseases, our ability to offer diagnostic tests for diseases may depend on the ability of third parties to discover particular sequences or markers and correlate them with disease, as well as the rate at which such discoveries are made. Our ability to design products that target these diseases may depend on our ability to obtain the necessary access to raw materials or intellectual property rights from third parties who make any of these discoveries. If we are unable to access new technologies or the rights to particular sequences or markers necessary for additional diagnostic products on commercially reasonable terms, we may not be able to develop new diagnostic products or enter new markets.

The sales cycles for our Ibis T5000 Biosensor Systems are lengthy, and we may expend substantial funds and management effort with no assurance of successfully selling our Ibis T5000 Biosensor Systems or services.

The sales cycles for Ibis T5000 Biosensor Systems are typically lengthy. Our sales and licensing efforts, and those of our partners, will require the effective demonstration of the benefits, value, and differentiation and validation of our products and services, and significant training of multiple personnel and departments within a potential customer organization. We or our partners may be required to negotiate agreements containing terms unique to each prospective customer or licensee, which would lengthen the sales cycle. We may expend substantial funds and management effort with no assurance that we will sell our products. In addition, this lengthy sales cycle makes it more difficult for us to accurately

forecast revenue in future periods and may cause revenues and operating results to vary significantly in future periods.

If we or our partners are required to obtain regulatory approval for our Ibis T5000 Biosensor System applications, we may not successfully obtain approval.

Depending on their intended use, our Ibis T5000 Biosensor Systems may be regulated as a medical device by the FDA and comparable agencies of other countries and require either premarket approval (PMA) or 510(k) clearance from the FDA, prior to marketing. The 510(k) clearance process usually takes from three to twelve months from submission, but can take longer. The premarket approval process is much more costly, lengthy, uncertain and generally takes from six months to two years or longer from submission. In addition, commercialization of any diagnostic or other product that our licensees or collaborators or we develop would depend upon successful completion of preclinical testing and clinical trials. Preclinical testing and clinical trials are

long, expensive and uncertain processes, and we do not know whether we, our licensees or any of our collaborators, would be permitted or able to undertake clinical trials of any potential products. It may take us or our licensees or collaborators many years to complete any such testing, and failure could occur at any stage. Preliminary results of trials do not necessarily predict final results, and acceptable results in early trials may not be repeated in later trials. We or our collaborators may encounter delays or rejections of potential products based on changes in regulatory policy for product approval during the period of product development and regulatory agency review.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

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

ITEM 4. CONTROLS AND PROCEDURES

As of the end of the period covered by this Quarterly Report on Form 10-Q, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective as of September 30, 2006. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 30, 2006.

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

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

PART II – OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

Ajinomoto Co., Inc. v. Isis Pharmaceuticals, Inc. On or about January 27, 2005, Ajinomoto Co., Inc., or Ajinomoto, filed a Demand for Arbitration against us with the American Arbitration Association in San Diego, California. The Demand related to a February 17, 1994 license agreement between Ajinomoto and us, that licensed certain intellectual property, including United States Patent No. 5,013,830, or the '830 patent, in exchange for initial payments, royalties and certain milestone payments relating to the development of products covered by the license. Ajinomoto alleged that several products developed by us are covered by the '830 patent, and thus by the license. In September 2006, Isis and Ajinomoto entered into a Settlement and Non-Exclusive License Agreement. Accordingly, Isis has recorded a $418,000 charge, which represents the present value of Isis' liability under this agreement.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

Not applicable

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

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

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Manufacturing, Commercialization and Development Agreement between the Company and Bruker Daltonics, Inc. dated July 31, 2006 (with certain confidential information deleted).

31.1	Certification by Chief Executive Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification by Chief Financial Officer Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification Pursuant to 18 U.S.C. Section 1350 as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.

Isis Pharmaceuticals, Inc.

(Registrant)

SIGNATURES

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

Signatures	Title	Date
/s/ Stanley T. Crooke Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	November 7, 2006
/s/ B. Lynne Parshall B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	November 7, 2006

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

MANUFACTURING, COMMERCIALIZATION AND DEVELOPMENT AGREEMENT

THIS MANUFACTURING, COMMERCIALIZATION AND DEVELOPMENT AGREEMENT (this "Agreement") is entered into as of July 31, 2006 (the "Effective Date") between ISIS PHARMACEUTICALS, INC., a Delaware corporation, through its IBIS BIOSCIENCES division ("Ibis"), and BRUKER DALTONICS INC., a Delaware corporation ("Bruker").

BACKGROUND

Bruker has expertise in manufacturing, promoting, supplying, installing and servicing analytical instruments (including mass spectrometers). Ibis has invented and created a system to identify infectious agents, a component of which is a mass spectrometer, and wishes to commercialize this system, referred to herein as the T5000 System. Bruker and Ibis wish to establish a strategic alliance under which Ibis will commit to deploying T5000 Systems incorporating Bruker's mass spectrometer, Bruker will manufacture, promote, supply, install and service T5000 Systems and the parties will use Bruker's contacts with government and non-government entities in Europe and the Middle East, as well as its global infrastructure and expertise in processing systems and consumables orders and supporting customers.

Accordingly, during the Term, Bruker will be the exclusive supplier of mass spectrometers for use in T5000 Systems and the exclusive manufacturer of T5000 Systems. In addition, Bruker will be the exclusive promoter and supplier of T5000 Systems (and consumables used to operate T5000 Systems) to government entities in Europe and the Middle East. Bruker will also be a non-exclusive promoter and supplier of T5000 Systems and consumables to non-government entities in Europe and the Middle East and will support Ibis' promotion efforts in North America. Bruker will be entitled to buy consumables for T5000 Systems from Ibis at a discount and resell such consumables to its customers.

Bruker will be responsible for processing and fulfilling orders for T5000 Systems originating from, and delivering T5000 Systems to, customers in North America, Europe and the Middle East. Bruker will be responsible for hardware-related issues (as described herein) originating in North America, Europe and the Middle East, and will be the point-of-contact for consumables- and software-related issues (as described herein) originating in Europe and the Middle East. Ibis will be responsible for consumables- and software-related issues originating in North America. The parties will also have certain training and other responsibilities as set forth herein.

In consideration of the foregoing premises, the mutual covenants contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto, intending to be legally bound, hereby agree as follows:

ARTICLE 1

DEFINITIONS

1.1 Definitions. For purposes of this Agreement (including its exhibits and schedules), capitalized terms used herein not otherwise defined herein will have the meanings set forth on Exhibit A.

ARTICLE 2

TECHNOLOGY TRANSFER PERIOD

2.1 Overview. To fulfill the commercialization objectives of this Agreement, Ibis will need to train Bruker on the Ibis Technology, including manufacture of the Ibis Amplicon Desalting Module and operation of the Ibis Analytical Systems. In addition, prior to the Technology Transfer Date, Ibis may receive indications of interest to purchase or may negotiate the sale of T5000 Systems. Ibis will have sole discretion whether to supply any such T5000 Systems. If Ibis decides to supply any such T5000 Systems, it will be on the terms set forth in this Article 2.

2.2 Technology Transfer Plan. The parties will establish a Technology Transfer Management Committee that will manage and ensure the successful transfer of the Ibis Technology to Bruker. The TMC will make decisions by unanimous vote and will be comprised of an equal number of individuals from each party with the background necessary to transfer the Ibis Technology as quickly as possible. In particular, the TMC will: (a) prepare and approve a plan setting forth the parties' respective rights and responsibilities with respect to transferring the Ibis Technology to Bruker (the "Technology Transfer Plan") and (b) set a date by which Bruker will assume full responsibility for the manufacture of T5000 Systems (including the Ibis Amplicon Desalting Module) and its other responsibilities as set forth herein, which date will be within 6 months of the Effective Date (the "Technology Transfer Date").

2.3 Technology Transfer Purchase Order Plan. The TMC will prepare and approve a plan setting forth the parties' respective rights and responsibilities with respect to orders for T5000 Systems and Ibis Consumables received prior to the Technology Transfer Date (the "Technology Transfer Purchase Order Plan"). The Technology Transfer Purchase Order Plan will address, among other things: (a) processing of orders (which will be by Bruker and in a similar manner as it processes orders for its own comparable products), (b) terms and conditions related to Bruker's delivery of MicrOTOFs and Ibis delivery of Ibis Amplicon Desalting Modules to the customer site and (c) responsibility for assembly and Installation of, training on, and service and support for, T5000 Systems (including transition of responsibility, if any).

2.4 Responsibilities. Each party will use commercially reasonable efforts in performing its obligations under the Technology Transfer Plan and the Technology Transfer Purchase Order Plan. Without limiting the foregoing, (a) the parties will cooperate and provide the data and assistance reasonably necessary to enable Bruker to assume full responsibility for the manufacture of T5000 Systems by the Technology Transfer Date, (b) Ibis will provide Bruker with access to a full technical data package for T5000 Systems, including drawings

prepared by Omnica Corporation related to T5000 Systems, and (c) Ibis will authorize the Omnica Corporation to sell the equipment related to the T5000 to Bruker under the same terms and pricing provided to Ibis.

2.5 Costs and Expenses; Revenue Sharing. Each party will bear its own costs (including those related to labor, materials and other expenses) associated with performing under the Technology Transfer Plan and the Technology Transfer Purchase Order Plan. System Revenues generated from the sale of any such T5000 Systems will be subject to the revenue sharing provisions set forth in Section 5.2.

2.6 Term. The TMC will complete all of its tasks under this Article 2 prior to the Technology Transfer Date.

ARTICLE 3

RIGHTS AND RESPONSIBILITIES; COMMERCIALIZATION PLAN

3.1 Rights. Subject to the terms and conditions of this Agreement (including Section 3.3, 3.4, 3.5, 11.2 and 11.3), for the Term Ibis hereby appoints Bruker as, and Bruker hereby accepts appointment as:

3.1.1 As of the Effective Date, exclusive supplier of mass spectrometers for use in T5000 Systems.

3.1.2 As of the Technology Transfer Date, exclusive manufacturer of T5000 Systems for all uses, except IVD Use, throughout the world.

3.1.3 As of the Effective Date, exclusive promoter, seller/reseller and supplier of T5000 Systems and Ibis Consumables for Government Use in the countries comprising the European/Middle East Territory.

3.1.4 As of the Effective Date, non-exclusive promoter, seller/reseller and supplier of T5000 Systems and Ibis Consumables for Other Use by End Users located in the European/Middle East Territory.

For clarification, Bruker will not have any rights to manufacture, promote, sell/resell or supply T5000 Systems or Ibis Consumables nor any responsibility to install and service any T5000 Systems, for any IVD Use.

3.2 Commercialization Plan.

3.2.1 Overview. To implement the general framework set forth in this Agreement, the parties must define the specifics of each party's rights and responsibilities with respect to the various tasks contemplated herein. Exhibit B sets forth the scope of each party's responsibilities, specific responsibilities of each party and topics that need to be addressed by the parties.

3.2.2 Commercialization Plan. Subject to the provisions described under

"Scope of Responsibilities" and "Specific Responsibilities" in Exhibit B, the parties will, prior to the Technology Transfer Date, mutually agree on a more detailed commercialization plan (the "Commercialization Plan") that is consistent with the overall intent of this Agreement and the scope and specific responsibilities set forth under "Scope of Responsibilities" and "Specific Responsibilities" in Exhibit B and that addresses the items described under "Topics to Address" in Exhibit B and such other items that are consistent with the foregoing.

3.2.3 Responsibilities. Each party will use commercially reasonable efforts in performing its obligations under the Commercialization Plan.

3.2.4 Costs and Expenses. Each party will bear its own costs (including those related to labor, materials and other expenses) associated with performing under the Commercialization Plan.

3.2.5 Conflicts. For clarification, in the event of any inconsistency between this Agreement and the Commercialization Plan, the terms and conditions of this Agreement will govern and control.

3.3 Existing Agreements; U.S. Government; Internal Use. Section 3.1 and anything in the Commercialization Plan to the contrary notwithstanding, Ibis retains the right to manufacture, promote, sell and supply, as well as process and fulfill orders for and deliver and Install, T5000 Systems (with or without additional components) (a) pursuant to any agreement initially entered into prior to the Effective Date, (b) to the U.S. Government (or any contractor or subcontractor thereof) pursuant to any agreement (including grants and subcontracts) (i) initially entered into prior to the Effective Date, (ii) that result from proposals or similar submissions submitted by Ibis prior to the Effective Date or (iii) that do not permit Ibis to subcontract with Bruker or (c) for the internal use of Ibis and its Affiliates; provided, however, that Ibis has the option to require Bruker to manufacture, promote and sell, process and fulfill orders for, supply, deliver, Install, provide training on, service and support and provide Updates for such T5000 Systems on the terms and conditions set forth herein. In the event Ibis exercises such option, Ibis will direct the relevant party to submit an order directly to Bruker.

3.4 Territorial Limitation. Section 3.1 notwithstanding, Bruker will not promote, sell, supply, deliver or Install (or cause to be promoted, sold, supplied, delivered or Installed) any T5000 System or Ibis Consumables outside the North American Territory and the European/Middle East Territory except in compliance with Section 3.5. If Bruker receives an indication of interest or order from a prospective purchaser for T5000 Systems or Ibis Consumables that would require supplying, delivering or Installing T5000 Systems or Ibis Consumables, as applicable, in a location outside the North American Territory or the European/Middle East Territory, Bruker will immediately inform Ibis and, subject to Section 3.5, the Ibis President and a vice president- or president-level officer of Bruker will consider the potential transaction.

3.5 Expansion of Rights and Responsibilities. In the event either party wishes to expand the scope of Bruker's rights set forth in Section 3.1 (and correlative obligations) or alter, expand or reduce the scope and specific responsibilities set forth under "Scope of Responsibilities" or "Specific Responsibilities" in Exhibit B, the Ibis President and a vice

president- or president-level officer of Bruker will discuss such expansion in good faith and any agreed upon expansion will be mutually agreed to in writing.

ARTICLE 4

MICROTOFS AND MICROTOF PARTS

4.1 Supply.

4.1.1 In the event Ibis exercises its right under Section 3.3 to manufacture, promote, sell and supply T5000 Systems, Bruker will supply, deliver and sell to Ibis such quantities of MicrOTOFs for integration into such T5000 Systems as set forth in Ibis' purchase orders, pursuant to the pricing in Section 5.6. Such purchase orders will set forth the quantity and the desired delivery date and will otherwise be governed by Exhibit D (other than with respect to the warranty relating to such MicrOTOFs, which will be governed by Section 4.2).

4.1.2 During the Term, the Transition Term and for [***] years following the end of the Transition Term, in the event Ibis desires to service and support T5000 Systems (including any predecessor or similar systems that incorporate a MicrOTOF) supplied, delivered and/or installed by Ibis prior to the Effective Date or supplied, delivered and/or installed by Ibis after the Effective Date pursuant to its exercise of its rights under Section 3.3 and requires parts that Bruker commonly sells ("Part(s)"), Bruker will supply, deliver and sell to Ibis or its customers such kind and quantity of Parts for use in servicing and supporting such T5000 Systems or systems as set forth in Ibis' purchase orders, pursuant to the pricing in Section 5.6. Such purchase orders will set forth the quantity and the desired delivery date and will otherwise be governed by Exhibit D (other than with respect to the warranty relating to such Parts, which will be governed by Section 4.2).

4.2 Warranty.

4.2.1 Bruker will service and support the MicrOTOF integrated into each T5000 System described in Section 4.1.1 pursuant to the warranty accompanying such MicrOTOF. Anything in such warranty to the contrary notwithstanding, such warranty will (a) inure to the benefit of and be valid and enforceable by Ibis and/or the end user of each T5000 System described in Section 4.1.1 and (b) the warranty period will be for a period of [***] year beginning upon demonstration by Bruker that the MicrOTOF complies with its specification, but in any event not more than (i) [***] months after delivery to such end user or (ii) [***] months after delivery to Ibis.

4.2.2 Bruker will service and support the Parts supplied pursuant to Section 4.1.2 pursuant to the warranty accompanying such Parts (the "Parts Warranty"). Anything in the Parts Warranty to the contrary notwithstanding, the Parts Warranty will (a) inure to the benefit of and be valid and enforceable by Ibis and/or the end user of each T5000 System described in Section 4.1.2and (b) the warranty period will be for a period of [***] year beginning upon demonstration by Bruker that the applicable Part complies with its specification, but in any event not more than (i) [***] months after delivery to such end user or (ii) [***] months after delivery to Ibis.

4.3 Terms of Purchase and Sale. The parties will prepare and approve a plan setting forth the parties' respective rights and responsibilities with respect to supplying and delivering MicrOTOFs and Parts (the "MicrOTOF Delivery Plan"). The MicrOTOF Delivery Plan will address, among other things: (a) lead-time required by Bruker for timely delivery of MicrOTOFs and Parts, (b) terms of delivery of MicrOTOFs and Parts (including packing, transportation and insurance requirements as set forth in Exhibit D) and (c) other specific obligations and undertakings of each party related to the foregoing.

ARTICLE 5

REVENUE SHARING; PRICING; PAYMENT

5.1 Bruker Negotiated Sales of T5000 Systems. With respect to each sale of a T5000 System the price of which is negotiated by Bruker and for which (a) Bruker sells, delivers and Installs, trains End Users on, services and supports and provides Updates for such T5000 System (all as contemplated by the Commercialization Plan) and (b) Ibis fulfills its obligations as contemplated by the Commercialization Plan with respect to such T5000 System, Bruker will pay Ibis amounts based on the following percentages of System Revenues (subject to the following minimums), which amounts will be cumulative and in addition to any other payments to be made to Ibis under this Agreement:

5.1.1 [***]% of System Revenues for such T5000 System, but in no event less than $[***] per such T5000 System (unless specifically authorized in writing by the Ibis President for any particular End User); plus

5.1.2 [***]% of System Revenues for such T5000 System, but in no event less than $[***] per such T5000 System, if Ibis supplies and delivers the Ibis Amplicon Desalting Module; plus

5.1.3 [***]% of System Revenues for such T5000 System, but in no event less than $[***] per such T5000 System, if Ibis services and supports the Ibis Amplicon Desalting Module.

For clarification, for purposes of Section 5.1(b), Ibis' obligations under the Commercialization Plan are not specific to particular sales or deployments of T5000 Systems, but rather require Ibis to provide Bruker generally with the Ibis Analytical Systems that will be integrated with each particular sale and deployment of a T5000 System.

5.2 Ibis Negotiated Sales of T5000 Systems. With respect to each sale of a T5000 System (a) the price of which is negotiated by Ibis or an Ibis Partner and for which (i) Bruker sells, delivers and Installs, trains End Users on, services and supports and provides Updates for such T5000 System (all as contemplated by the Commercialization Plan) and (ii) Ibis fulfills its obligations under the Commercialization Plan with respect to such T5000 System or (b) under the Technology Transfer Purchase Order Plan, Bruker is entitled to retain the applicable percentage of System Revenues set forth below (subject to the

applicable minimum set forth below) and Bruker will pay Ibis any remaining amount resulting from such sale, which amounts will be in addition to any other payments to be made to Ibis under this Agreement:

5.2.1 If Ibis did not supply and deliver the Ibis Amplicon Desalting Module and is not servicing and supporting the Ibis Amplicon Desalting Module, [***]% of System Revenues for such T5000 System, but in no event less than $[***] per such T5000 System (unless specifically authorized in writing by Bruker by an authorized officer for any particular End User); or

5.2.2 If Ibis did supply and deliver the Ibis Amplicon Desalting Module but is not servicing and supporting the Ibis Amplicon Desalting Module, [***]% of System Revenues for such T5000 System, but in no event less than $[***] per such T5000 System (unless specifically authorized in writing by Bruker by an authorized officer for any particular End User); or

5.2.3 If Ibis did supply and deliver the Ibis Amplicon Desalting Module and is servicing and supporting the Ibis Amplicon Desalting Module, [***]% of System Revenues for such T5000 System, but in no event less than $[***] per such T5000 System (unless specifically authorized in writing by Bruker by an authorized officer for any particular End User).

For clarification, for purposes of Section 5.2(a)(ii), Ibis' obligations under the Commercialization Plan are not specific to particular sales or deployments of T5000 Systems, but rather require Ibis to provide Bruker generally with the Ibis Analytical Systems that will be integrated with each particular sale and deployment of a T5000 System.

5.3 Ibis Sales of T5000 Systems (Other than Full Bruker Participation). For each sale of a T5000 System the price of which is negotiated by Ibis or an Ibis Partner but not covered by Section 5.2 (that is, Bruker does not perform all of the tasks assumable by Bruker as set forth in the Commercialization Plan), Ibis and Bruker, in accordance with Section 15.10, will determine an equitable allocation of System Revenues based on obligations assumed by Ibis (either directly or through a Third Party, including an Ibis Partner).

5.4 Bruker Purchase of Ibis Consumables. Solely in connection with satisfying its obligations under the Commercialization Plan, beginning on the Effective Date Bruker may purchase, and Ibis will sell, Ibis Consumables at [***]% of Ibis' then current list price for such Ibis Consumables in the United States. However, if Ibis discounts particular Ibis Consumables by more than [***]% from its current list price in the United States for purchases of the same or similar Ibis Consumables in the same or similar volume, then Bruker may purchase, and Ibis will sell, Ibis Consumables at [***]% of Ibis average selling price in the United States for purchases of the same or similar Ibis Consumables in the same or similar volume. Notwithstanding the foregoing, the parties understand and agree that Ibis may, from time to time, provide discounted Ibis Consumables to customers who will be supplying data to Ibis for marketing, regulatory or other valuable purposes or in connection with a significant relationship. Such discounted Ibis Consumables will not be included in calculating such average price; provided, however, that in any case not more than [***]% of Ibis Consumables sales will be excluded from the calculation of such average price.

5.5 Extended Warranty. (a) For each Extended Warranty sold to an End User located in the North American Territory, Bruker will pay Ibis [***]% of Extended Warranty Revenues (provided Ibis fulfills its obligations under the Commercialization Plan with respect to

providing Bruker with Renewal Updates), but in no event less than $[***] for each year of coverage under such Extended Warranty (unless specifically authorized in writing by the Ibis President for any particular End User or any particular defined business incentive) and (b) for each Extended Warranty sold to an End User located outside the North American Territory, Bruker will pay Ibis [***]% of Extended Warranty Revenues (provided Ibis fulfills its obligations under the Commercialization Plan with respect to providing Bruker with Renewal Updates), but in no event less than $[***] for each year of coverage under such Extended Warranty (unless specifically authorized in writing by the Ibis President for any particular End User or any particular defined business incentive). Bruker acknowledges and agrees that these payments are tied to each Extended Warranty sold to an End User for each T5000 System purchased by such End User for each year of coverage under such Extended Warranty. For clarification, (c) for purposes of Section 5.5(a), Ibis' obligations under the Commercialization Plan with respect to providing Bruker with Renewal Updates are not specific to particular sales of Extended Warranties, but rather require Ibis to provide Bruker generally with Renewal Updates that will be integrated with each particular sale of an Extended Warranty and (d) Bruker has no obligation to compensate Ibis for providing Renewal Updates other than as set forth in Section 5.5(a) and (b).

5.6 MicrOTOFs; Parts. Bruker will sell MicrOTOFs to Ibis pursuant to Section 4.1.1 at a fixed price of $[***] per MicrOTOF and, during the Term, the Transition Term and for [***] years following the end of the Transition Term, will sell Parts to Ibis pursuant to Section 4.1.2 at [***]% of Bruker's then-current list price for such Parts in the United States.

5.7 Payment Terms.

5.7.1 All payments by Bruker under Section 5.1, 5.2, 5.3 and 5.5 will be calculated based on System Revenues and Extended Warranty Revenues, as applicable. Ibis' share of System Revenues are due and payable within 30 days of the end of the calendar month in which the initial Installation is complete. Ibis' share of Extended Warranty Revenues are due and payable within 30 days of the end of the each calendar month in which Bruker receives payment.

5.7.2 All payments by Bruker under Section 5.4 (for Ibis Consumables) and all payments by Ibis under Section 5.6 (for MicrOTOFs and Parts) are due and payable within [***] days of the invoice date.

5.7.3 All payments hereunder will be by check or wire transfer to a bank account designated by the party to whom such payment is due pursuant to instructions provided by such party.

5.7.4 All payments hereunder and System Revenues calculations and Extended Warranty Revenues calculations will be reflected in United States dollars. If any currency conversion is required to reflect System Revenues or Extended Warranty Revenues in United States dollars, such

conversion will be made by using the average of the exchange rates for the purchase and sale of United States dollars as published in *The Wall Street Journal*, Eastern Edition, on the last business day of the calendar month to which a payment relates.

5.7.5 Any payments under this Agreement that are not paid when due will bear interest to the extent permitted by applicable law at the prime rate as reported by the Bank of America, New York, New York, on the date such payment is due, plus an additional 12% simple interest per annum, calculated on the number of days such payment is delinquent and a 365 day year; provided, however, that in no event will such rate exceed the maximum legal interest rate allowed by law. The party from whom the payment is due will pay all costs and expenses incurred by the party to whom payment is due in collecting delinquent amounts (including late charges), including attorneys' fees and costs. The party to whom the payment is due may accept partial payment by the party from whom the payment is due, which will not constitute a waiver of the right of the party to whom the payment is due to collect the balance. This Section 5.7.5 will in no way limit any other remedies available to any party.

5.8 Reports. Each payment under Section 5.1, 5.2 and 5.5 will be accompanied by a report of System Revenues and Extended Warranty Revenues during the calendar month related to such payment. Such report will be in sufficient detail so as to permit confirmation of the accuracy of payments made, including (as applicable) amounts invoiced/purchase orders received, initial Installations completed, gross receipts, applicable deductions, the applicable percentage applied and the aggregate payment due to Ibis for such calendar month.

5.9 Taxes. The party making payment hereunder will pay any and all taxes levied on account of such payment. If laws or regulations require that taxes be withheld, the party making such payment will (a) timely pay the taxes to the proper taxing authority, and (b) send proof of payment to the party receiving such payment and certify its receipt by the tax authorities within 60 days following that payment.

5.10 Records; Audits.

5.10.1 Records. Bruker will keep, and will require its Affiliates to keep, complete, true and accurate books and records (a) pertaining to the sale or other disposition of T5000 Systems, Ibis Consumables and Extended Warranties in sufficient detail to permit confirmation of the accuracy of all payments due hereunder and (b) of Systems Revenues and Extended Warranty Revenues in accordance with United States generally accepted accounting principles in sufficient detail to permit confirmation of the accuracy of all payments due hereunder. Bruker will keep such books and records for at least three years following the end of the calendar year to which they pertain.

5.10.2 Audit. Upon the written request of Ibis and not more than once in any 12-month period, Bruker will, and will require its Affiliates to, permit an independent certified public accounting firm of nationally recognized standing selected by Ibis to have access during normal business hours to such books and records of Bruker and its Affiliates as may be reasonably necessary to verify the accuracy of the reports under Section 5.8. The accounting firm will disclose to Ibis only whether the royalty reports are correct or incorrect and the specific details concerning any discrepancies. No other information will be provided to Ibis. If such accounting firm identifies a discrepancy made during such period, Bruker will pay Ibis the amount of the discrepancy within 30 days of the date that the Ibis delivers to Bruker such accounting firm's written report so concluding, or as otherwise agreed upon by the parties. The fees charged by such accounting firm will be paid by Ibis; provided, however, that if an audit

uncovers an underpayment of amounts due by Bruker under this Article 5 by more than 5% then (a) the fees of such accounting firm will be paid by Bruker and (b) such audit will not count as an audit for purposes of the frequency by which Ibis may audit Bruker's records under this Section 5.10.2.

5.10.3 Confidential Information. All financial information subject to review under this Section 5.10 will be treated as Confidential Information of Bruker and Ibis will cause its accounting firm to enter into an acceptable confidentiality agreement with Bruker obligating it to retain all such information in confidence (subject to reasonable exceptions).

ARTICLE 6

TRADEMARKS

6.1 Trademark Use.

6.1.1 Ibis' Marks. Subject to the terms and conditions of this Agreement and during the Term and the Transition Term, Ibis hereby grants Bruker a non-exclusive, non-transferable, royalty-free limited license to use Ibis' Marks in the North American Territory and the European/Middle East Territory solely in connection with the performance of its obligations under the Commercialization Plan. Ibis grants no rights other than those expressly granted hereunder, and Bruker hereby agrees to and recognizes Ibis' exclusive ownership of Ibis' Marks. Any use of Ibis' Marks will be in conformity with the trademark policy and other written instructions of Ibis.

6.1.2 Bruker Marks. Subject to the terms and conditions of this Agreement, during the Term and the Transition Term, Bruker hereby grants Ibis a non-exclusive, non-transferable, royalty-free limited license to use Bruker's Marks solely in connection with the performance of its obligations under the Commercialization Plan. Bruker grants no rights other than those expressly granted hereunder, and Ibis hereby agrees to and recognizes Bruker's exclusive ownership of Bruker's Marks. Any use of Bruker's Marks will be in conformity with the trademark policy and other written instructions of Bruker.

6.2 Maintenance of Marks. Each party will use the other party's Marks in compliance with all applicable laws, rules and regulations and in a manner that reflects favorably upon and preserves the integrity of such other party's Marks. Each party agrees not to (a) adopt or use any trademarks, brand names, words, logos, symbols, letters, designs or marks that would be confusingly similar to the other party's Marks, (b) modify any of the other party's Marks in any way, (c) use any of the other party's Marks on or in connection with any goods or services other than the T5000 Systems or (d) take any other action that could diminish the value of the other party's Marks or damage the goodwill and/or reputation for quality associated with such other party's Marks. Any goodwill arising out of the use by a party of the other party's Marks hereunder will inure to the benefit of the owner thereof. Each party agrees to provide the other party with a sample of all proposed marketing materials and any other materials utilizing the other party's Marks at least 30 days prior to use thereof.

ARTICLE 7

CONFIDENTIALITY

7.1 Confidentiality. Each party agrees during the Term, the Transition Term and for a period of four years after the end of the Transition Term that it will protect and hold the other party's Confidential Information in trust and confidence, that it will not use such Confidential Information in any manner or for any purpose not expressly set forth in this Agreement, and will not disclose any such Confidential Information to any Third Party without first obtaining the other party's express written consent on a case-by-case basis. A party may disclose Confidential Information of the other party to its own employees, consultants, agents and contractors (and only such employees, consultants, agents and contractors) having a "need to know" in connection with such party's proper performance hereunder.

7.2 Exceptions. Confidential Information of a disclosing party will not include information which the receiving party can demonstrate by competent written proof: (a) is now, or hereafter becomes, through no act or failure to act on the part of the receiving party, generally known or available, (b) is known by the receiving party at the time of receiving such information, as evidenced by its written records, (c) is hereafter furnished to the receiving party by a Third Party, as a matter of right and without restriction on disclosure or (d) is independently developed by the receiving party without the use of or reference to the disclosing party's Confidential Information.

7.3 Authorized Disclosure. Each party may disclose Confidential Information belonging to the other party to the extent such disclosure is reasonably necessary in the following instances: (a) complying with applicable court orders or governmental regulations and (b) disclosure to Affiliates, consultants, agents or other Third Parties in connection with due diligence or similar investigations by such parties, provided that any such person or entity agrees in writing to be bound by terms of confidentiality and non-use comparable in scope to those set forth in this Article 7. Notwithstanding the foregoing, in the event a party is required to make a disclosure of the other party's Confidential Information pursuant to Section 7.3(a), it will, except where impracticable, give reasonable advance notice to the other party of such disclosure and cooperate with the other party's efforts to secure confidential treatment of such information.

7.4 Return of Confidential Information. After termination or expiration of this Agreement, upon request, each party will return to the other party, or destroy, within 30 days of such request all Confidential Information received from the other party.

7.5 Remedies. In the event of any breach of this Article 7 by the receiving party, including, without limitation, the actual or threatened disclosure or unauthorized use of the disclosing party's Confidential Information without the prior express written consent of the disclosing party, the parties agree that the disclosing party would suffer an irreparable injury such that no remedy at law would adequately protect or appropriately compensate the disclosing party for such injury. Accordingly, the receiving party agrees that the disclosing party will have the right to enforce this Article 7 and any of its provisions by injunction, specific performance or other equitable relief, without bond and without prejudice to any other rights and remedies that the disclosing party may have for a breach of this Agreement.

7.6 Public Announcements. All publicity, press releases and other announcements relating to this Agreement will be reviewed in advance by, and subject to the approval of, both parties (which approval will not be unreasonably withheld); provided, however, that upon full execution of this Agreement either party may issue the press release set forth in Exhibit C; provided, further, that either party may disclose the terms of this Agreement insofar as required to comply with applicable securities laws.

ARTICLE 8

INTELLECTUAL PROPERTY

8.1 Ownership of Inventions. Except as otherwise set forth herein, ownership of any Invention will track inventorship, and the inventorship of any Invention will be determined in accordance with United States laws of inventorship. If any Invention is not patentable, inventorship will be determined as if it were patentable.

8.2 License to Ibis Technology Improvements. To the extent that any Improvements to the Ibis Technology are made by employees or agents of Bruker or its Affiliates that Bruker controls, Bruker hereby grants to Ibis a non-exclusive, fully-paid, royalty-free, worldwide, sublicensable and transferable, irrevocable and perpetual license under all right title and interest to exploit such Improvements for any purpose whatsoever (including commercial activities). For purposes of clarification, the foregoing license includes the right to (directly or through a third party) make, use, offer to sell, sell, import, reproduce, prepare derivative works, distribute copies, perform and/or display.

8.3 License to MicrOTOF Technology Improvements. To the extent that any Improvements to the MicrOTOF Technology are made by employees or agents of Ibis or its Affiliates that Ibis controls, Ibis hereby grants to Bruker a non-exclusive, fully-paid, royalty-free, worldwide, sublicensable and transferable, irrevocable and perpetual license under all right title and interest to exploit such Improvements for any purpose whatsoever (including commercial activities). For purposes of clarification, the foregoing license includes the right to (directly or through a third party) make, use, offer to sell, sell, import, reproduce, prepare derivative works, distribute copies, perform and/or display.

8.4 Pursuit of Joint Intellectual Property Rights. With respect to Inventions jointly conceived as a result of performing under this Agreement ("Joint Inventions"), the parties will negotiate in good faith regarding which party will be responsible for preparing, filing and prosecuting any patent applications or other appropriate filings and maintaining, enforcing and defending any patents, copyrights or other similar rights issued thereon (including the allocation of costs and awards related thereto).

8.5 Infringement by Third Parties. Each party will promptly notify the other in writing of any alleged or threatened infringement of any MicrOTOF Technology or Ibis Technology of which such party becomes aware. Both parties will use commercially reasonable efforts in cooperating with

each other to terminate such infringement without litigation, if appropriate. Other than any action or proceeding with respect to infringement of solely MicrOTOF Technology (which Bruker will have the sole right to bring and control at its own

expense and by counsel of its own choice; provided, however, that with respect to infringement of any MicrOTOF Technology that is likely to have a material and adverse effect on any T5000 System being developed or commercialized pursuant to this Agreement, Ibis will have the right to receive appropriate information relating to such action and to provide input to Bruker), Ibis will have the sole right to bring and control any action or proceeding with respect to infringement of T5000 Systems or Ibis Consumables at its own expense and by counsel of its own choice.

8.6 Infringement of Third Party Rights. Each party will promptly notify the other in writing of any allegation by a Third Party that the MicrOTOF Technology, the Ibis Technology, T5000 Systems, Ibis Consumables or the activity of either of the parties pursuant to this Agreement infringes or may infringe the intellectual property rights of such Third Party. Other than any such claim involving alleged infringement of Third Party rights solely by MicrOTOF Technology (which Bruker will have the sole right to control any defense of at its own expense and by counsel of its own choice; provided, however, that with respect to infringement of any MicrOTOF Technology that is likely to have a material and adverse effect on any T5000 System being developed or commercialized pursuant to this Agreement, Ibis will have the right to receive appropriate information relating to such action and to provide input to Bruker), Ibis will have the sole right to control the defense of any such claim involving alleged infringement of Third Party rights by T5000 Systems, Ibis Consumables or the activity of either of the parties pursuant to this Agreement.

8.7 Limited Rights; No Challenge. Neither party will have the right to acquire any rights in or is entitled to use, sell, copy, license or otherwise exploit the other party's Intellectual Property Rights other than as expressly set forth herein. Under no circumstances will either party challenge or assist a Third Party to challenge the other party's rights in MicrOTOF Technology or Ibis Technology.

ARTICLE 9

REPRESENTATIONS AND WARRANTIES; DISCLAIMER

9.1 Mutual Representations and Warranties. Each party represents and warrants to the other party that (a) such party is duly organized, validly existing, and in good standing under the laws of the jurisdiction of its establishment or incorporation, (b) such party has taken all action necessary to authorize it to enter into this Agreement and perform its obligations under this Agreement, (c) this Agreement will constitute the legal, valid and binding obligation of such party, (d) neither the execution of this Agreement nor the performance of such party's obligations hereunder will conflict with, result in a breach of, or constitute a default under any provision of the organizational documents of such party, or of any law, rule, regulation, authorization or approval of any government entity, or of any agreement to which it is a party or by which it is bound and (e) it has and will maintain all government permits, including without limitation health, safety and environmental permits, necessary for the conduct of the actions and procedures that it undertakes pursuant to this Agreement.

9.2 Disclaimer. Except as expressly set forth herein, EACH PARTY EXPRESSLY DISCLAIMS ANY AND ALL WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED,

INCLUDING WITHOUT LIMITATION THE WARRANTIES OF DESIGN, MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, NON-INFRINGEMENT OF THE INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES OR ARISING FROM A COURSE OF DEALING, USAGE OR TRADE PRACTICES.

9.3 Limitation of Liability. EXCEPT FOR LIABILITY FOR BREACH OF ARTICLE 7, NEITHER PARTY SHALL BE ENTITLED TO RECOVER FROM THE OTHER PARTY ANY INDIRECT, SPECIAL, INCIDENTAL, CONSEQUENTIAL OR PUNITIVE DAMAGES IN CONNECTION WITH THIS AGREEMENT; PROVIDED, HOWEVER, THAT THIS SECTION 9.3 SHALL NOT BE CONSTRUED TO LIMIT EITHER PARTY'S INDEMNIFICATION RIGHTS OR OBLIGATIONS UNDER ARTICLE 12. THE PARTIES AGREE THAT PAYMENTS ACCRUED AND PAYABLE UNDER ARTICLE 5, TO THE EXTENT NOT PAID AS AND WHEN REQUIRED PURSUANT TO THIS AGREEMENT, ARE DIRECT DAMAGES (NOT INDIRECT, SPECIAL, INCIDENTAL, CONSEQUENTIAL OR PUNITIVE).

ARTICLE 10

CERTAIN COVENANTS

10.1 Non-Solicitation. During the Term, the Transition Term and for [***] following the end of the Transition Term, neither party nor any of its Affiliates will solicit or seek to employ any person who is an employee of the other party or its Affiliates as of the Effective Date or becomes an employee of the other party or its Affiliates during the Term or the Transition Term; provided, however, that the foregoing provision will not prevent either party or its Affiliates from hiring employees of the other party or its Affiliates who respond to general employment advertising or similar public solicitations or employing any such person who contacts such party or its Affiliates on his or her own initiative without any direct or indirect solicitation by or encouragement from such party or its Affiliates.

10.2 Non-Compete. During the Term and the Transition Term, neither Bruker nor any of its Affiliates will (whether internally or in active collaboration with any Third Party(ies)), develop, manufacture, promote, sell or supply any complete system that is designed to perform electrospray ionization orthogonal-TOF analysis of PCR products substantially as a T5000 System without the express written consent of Ibis; provided, however, that Bruker has no restriction whatsoever in developing, selling and servicing its general purpose electrospray orthogonal-TOF mass spectrometer to any customer.

10.3 Exclusive Source. During the Term, the Transition Term and for two years following the end of the Transition Term, neither Bruker nor any of its Affiliates will directly or indirectly sell any (a) primers and related reagent solutions or (b) analysis software or databases for use with the T5000 System other than those purchased from Ibis.

10.4 Treatment of End Users. In terms of priority in internal processes and/or in terms of customer support and service, each party will treat all End Users equally and will not favor any particular End User over another. For clarification, this Section 10.4 will not prevent

either party from providing quantity discounts, preferred T5000 Systems pricing or other similar arrangements to End Users.

10.5 Assurances. Neither party will structure transactions with Third Parties in an attempt to avoid payment obligations to the other party. For clarification, neither party will offer Third Parties terms that encourage such Third Party to purchase T5000 Systems or Ibis Consumables at reduced prices in exchange for consideration that does not ratably benefit both parties as set forth herein. Such terms include financial and non-financial terms, including incentives, discounts, rebates, perquisites, extended warranties (whether in scope, duration or otherwise), enhanced service, more favorable return policies and most favored pricing.

ARTICLE 11

TERM AND TERMINATION

11.1 Term. Unless earlier terminated pursuant to this Article 11 and subject to Sections 11.2 and 11.3, the term of this Agreement will commence on the Effective Date and continue until the fourth anniversary of the Effective Date (the "Initial Term"). After the Initial Term, this Agreement will automatically renew for additional [***] year periods (the "Extension Terms") unless either party gives written notice of termination at least [***] months prior to the expiration of the Initial Term or of one of the Extension Terms. The foregoing notwithstanding, Bruker and Ibis each will continue to satisfy its obligations under each Extended Warranty (as set forth in the Commercialization Plan) until the expiration or termination of such Extended Warranty pursuant to its terms.

11.2 Transition Term. Subject to Section 11.3, following the end of the Term, Bruker may, until the [***] anniversary of the end of the Term (the "Transition Term") and on the same terms and conditions as applied during the Term, continue to (a) purchase, resell and deliver Ibis Consumables (as set forth in the Commercialization Plan) to parties in both the Government Use market and the Non-Exclusive Market with whom it consummated the sale of a T5000 System prior to the end of the Term and (ii) sell Extended Warranties and service and support for T5000 Systems (as set forth in the Commercialization Plan) to parties in both the Government Use market and the Non-Exclusive Market with whom it consummated the sale of a T5000 System prior to the end of the Term, and, during the Transition Term, Ibis will continue to fulfill its correlative obligations under the Commercialization Plan.

11.3 Partnering Transaction. Section 11.2 notwithstanding, in the event Ibis consummates a Partnering Transaction, Bruker may, at its election, transition its on-going rights and obligations in the Non-Exclusive Market to Ibis (or its designee) pursuant to a timeline and plan approved by the parties in accordance with Section 15.10; provided, however, that Bruker may not transition its obligations under Section 3.1.1 and 3.1.2 and correlative obligations under the Commercialization Plan or its obligations under any Extended Warranty without the prior written consent of Ibis (or its successor). If Bruker does not elect to transition such obligations, Isis may, at its election, terminate Bruker's rights under Section 11.2 in the Non-Exclusive Market after the later of (a) the [***] anniversary of the effective date of the Partnering Transaction and (b) the [***] anniversary of the Effective Date. For clarification, during the Term, even if Ibis consummates a Partnering Transaction, Bruker will remain the exclusive

supplier of mass spectrometers for use in T5000 Systems, the exclusive manufacturer of T5000 Systems for all uses, except IVD Use, throughout the world and the exclusive marketer of T5000 Systems, Ibis Consumables for Government Use.

11.4 Termination for Cause. A party will have the right to terminate this Agreement by providing written notice to the other party upon the occurrence of any of the following:

11.4.1 the other party (i) admits its inability to pay its debts as they come due, (ii) has a receiver appointed for all or of any part of its property, (iii) makes any assignment for the benefit of creditors or (iv) files a petition under any bankruptcy, insolvency or similar law, or any such petition is filed against such party and is not dismissed within 75 days; or

11.4.2 upon or after the breach of any material provision of this Agreement by the other party if the breaching party has not cured such breach within the 60 day (10 day with regard to any payment breach) period following written notice of breach by the non-breaching party.

11.5 Effect of Expiration or Termination.

11.5.1 Except as expressly set forth in this Section 11, upon the effectiveness of the expiration or termination of this Agreement for any reason, all rights and licenses granted under this Agreement will immediately terminate and any purchase orders not yet completely fulfilled may be canceled at the option of the party that received such order.

11.5.2 After the Term and/or the Transition Term, as applicable, Bruker will not represent or hold itself out as being an authorized distributor or otherwise having any rights to commercialize the T5000 Systems or Ibis Consumables or engage in any practices that might make it appear that Bruker has any such rights. After the Term and/or the Transition Term, as applicable, Ibis will not represent or hold itself out as being an authorized distributor or otherwise having any rights to commercialize the MicrOTOF or MicrOTOF II or engage in any practices that might make it appear that Ibis has any such rights.

11.5.3 In the event this Agreement is terminated pursuant to Section 11.4.2 due to Bruker's breach of its obligations hereunder to perform service and support for End Users of T5000 Systems, Bruker will, if requested by Ibis, assign to Ibis Bruker's rights to perform service and support with respect to T5000 Systems for such End Users and will transfer to Ibis any prepayment Bruker has received therefor. The rights of Ibis and obligations of Bruker in this Section 11.5.3 will apply only to the extent the applicable service and support agreement between Bruker and the End User pertains solely to T5000 Systems and not other products distributed by Bruker.

11.6 Survival. Notwithstanding anything to the contrary herein, the following provisions will survive the expiration or termination of this Agreement for any reason: Article 4, Sections 5.4, 5.6, 5.7, 5.8, 5.9 and 5.10, Article 7, Sections 8.1, 8.2, 8.3, 8.7, 9.2, 9.3, 10.1, 10.3, 11.1, 11.5 and 11.6 and Articles 12, 13 and 15. In addition, Sections 10.2 and 11.2 will survive until the end of the Transition Term and Section 11.3 will survive until the later of (a) the second anniversary of the effective date of the Partnering Transaction or (b) the fourth anniversary of the Effective Date. It is expressly understood and agreed that, notwithstanding anything to the

contrary herein, any payment rights and obligations accruing under Article 5 prior to expiration or termination will continue unaffected and survive expiration or termination of this Agreement for any reason.

ARTICLE 12

INDEMNIFICATION

12.1 Indemnification by Bruker. Bruker hereby agrees to save, defend and hold Ibis and its Affiliates and their respective directors, officers, employees and agents (each, an "Ibis Indemnitee") harmless from and against any and all claims, suits, actions, demands, liabilities, expenses and/or loss, including reasonable legal expense and attorneys' fees, with respect to subparts (a) and (b) below solely with respect to personal injury and property damage (collectively, "Losses"), to which any Ibis Indemnitee may become subject as a result of any claim, demand, action or other proceeding by any Third Party to the extent such Losses arise directly out of (a) the breach by Bruker of any warranty, representation, covenant or agreement made by Bruker in this Agreement, (b) any act or omission pursuant to this Agreement by Bruker; except, in each case, to the extent such Losses result from the gross negligence or willful misconduct of any Ibis Indemnitee or the breach by Ibis of any warranty, representation, covenant or agreement made by Ibis in this Agreement or (c) a claim that any product or service provided by Bruker (including the MicrOTOF) infringes the intellectual property of a Third Party (unless such claim is based on use of a product provided by Bruker in combination with other hardware, software, firmware or materials not provided by Bruker where, without such combination, there would be no infringing activity).

12.2 Indemnification by Ibis. Ibis hereby agrees to save, defend and hold Bruker and its Affiliates and their respective directors, officers, employees and agents (each, a "Bruker Indemnitee") harmless from and against any and all Losses to which any Bruker Indemnitee may become subject as a result of any claim, demand, action or other proceeding by any Third Party to the extent such Losses arise directly out of (a) the breach by Ibis of any warranty, representation, covenant or agreement made by Ibis in this Agreement, (b) any act or omission pursuant to this Agreement by Ibis; except, in each case, to the extent such Losses result from the gross negligence or willful misconduct of any Bruker Indemnitee or the breach by Bruker of any warranty, representation, covenant or agreement made by Bruker in this Agreement or (c) a claim that any product or service provided by Ibis (including the Ibis Amplicon Desalting Module) infringes the intellectual property of a Third Party (unless such claim is based on use of a product provided by Ibis in combination with other hardware, software, firmware or materials not provided by Ibis where, without such combination, there would be no infringing activity).

12.3 Control of Defense. Any entity entitled to indemnification under this Article 12 will give notice to the indemnifying party of any Losses that may be subject to indemnification, promptly after learning of such Losses, and the indemnifying party may assume the defense of such Losses with counsel reasonably satisfactory to the indemnified party. If such defense is assumed by the indemnifying party with counsel so selected, the indemnifying party will not be subject to any liability for any settlement of such Losses made by the indemnified party without the indemnifying party's consent (but such consent will not be unreasonably withheld,

conditioned or delayed), and will not be obligated to pay the fees and expenses of any separate counsel retained by the indemnified party with respect to such Losses.

12.4 Insurance. Each party, at its own expense, will maintain product liability insurance in an amount consistent with industry standards during the Term, the Transition Term and for 2 years following the end of the Transition Term with respect to T5000 Systems and Ibis Consumables it delivers to End Users. Each party will provide a certificate of insurance evidencing such coverage to the other party upon request and will provide the other party with written notice at least 15 days prior to the cancellation, non-renewal or material change in such insurance. The amounts of any insurance coverage obtained pursuant to this Section 12.4 will not be construed to create a limit on any party's liability with respect to its indemnification obligations hereunder.

ARTICLE 13

DISPUTE RESOLUTION

13.1 Dispute Resolution. The parties recognize that disputes as to certain matters may arise from time-to-time. It is the objective of the parties to seek to resolve any disputes arising under this Agreement in an expedient manner and, if at all possible, without resort to litigation, and to that end the parties agree to abide by the following procedures set forth in this Article 13 to resolve any such disputes. The parties initially will attempt to settle any such dispute through good faith negotiations in the spirit of mutual cooperation between business executives with authority to resolve the dispute.

13.2 Escalation. Prior to taking action as provided in Section 13.3 or 13.4 of this Agreement, if the parties cannot resolve a dispute within 20 days of written request by either party to the other, the parties will first submit such dispute to the Executive Vice President of Isis Pharmaceuticals, Inc. or the Ibis President and a vice-president- or president-level officer of Bruker with authority to settle the applicable dispute, for resolution. Such officers will meet promptly thereafter and will negotiate in good faith to resolve such dispute. If they cannot resolve such dispute within 30 days of commencing such negotiations, then the matter will be submitted to mediation in accordance with Section 13.3. All negotiations pursuant to this Section 13.2 will be confidential and will be treated as compromise and settlement negotiations for purposes of applicable rules of evidence.

13.3 Mediation. If the parties cannot resolve the dispute pursuant to Section 13.2, then upon the expiration of the 30 day period for negotiation between the officers of the parties pursuant to Section 13.2, the parties will jointly commence mediation by providing to the American Arbitration

Association ("AAA") a joint written request for mediation, setting forth the subject matter of the dispute and the relief requested by each party. The parties will cooperate with the AAA and with one another in selecting a mediator from AAA's panel of neutral mediators and in scheduling the mediation proceedings which must, in any event, occur within 30 days after the submission of the parties' joint written request for mediation. The parties covenant that they will participate in at least one full day of mediation in good faith and that they will share equally in its costs. If mediation fails to resolve such dispute, either party may submit such dispute to a court having competent jurisdiction.

13.4 Court Actions. Notwithstanding the above, to the full extent allowed by law, either party may bring an action in any court of competent jurisdiction for injunctive relief (or any other provisional remedy) to protect the parties' rights or enforce the parties' obligations under this Agreement pending final resolution of any claims related thereto in a mediation as provided above. In addition, either party may bring an action in any court of competent jurisdiction to resolve disputes pertaining to the validity, construction, scope, enforceability, infringement or other violations of patents or other proprietary or intellectual property rights. The parties will use their reasonable efforts to conduct all dispute resolution procedures under this Agreement as expeditiously, efficiently and cost-effectively as possible.

ARTICLE 14

EXPORT COMPLIANCE

14.1 Export Regulations. The parties acknowledge and agree that all Ibis deliveries under this Agreement will be to a location within the United States. Bruker will be solely responsible for complying with and will ensure compliance with any and all export laws, rules and regulations; provided, however, that Ibis will be solely responsible for classifying the T5000 System (including the Ibis Analytical Systems and whether as an assembled instrument or in its component parts), including whether the T5000 Systems is a "defense article" (under the Arms Export Contract Act, its implementing regulations and regulations promulgated thereunder) and the appropriate export control classification number(s) (under the Export Administration Act, its implementing regulations and regulations promulgated thereunder), and Bruker will reasonably assist Ibis in determining such classification. Bruker understands that Ibis is subject to regulation by agencies of the Government, including the United States Department of Commerce, Office of Foreign Assets Control of the United States Treasury and the United States Department of Defense, which prohibit export or diversion of certain technical products and services to certain countries, even if such products or services were not manufactured or assembled in the United States. Bruker warrants that it will comply in all respects with the Export Administration Regulations, International Traffic in Arms Regulation and all other export and re-export restrictions applicable hereto.

ARTICLE 15

GENERAL PROVISIONS

15.1 Assignment. Neither party may assign this Agreement or any rights or obligations hereunder, by operation of law or otherwise, without the prior written approval of the other party; provided, however that a party may make such an assignment without consent to Affiliates or to a successor to all of or substantially all of the business or assets of such party to which this Agreement relates, whether in a merger, sale of stock, sale of assets or other transaction. The rights and obligations of the parties under this Agreement will be binding upon and inure to the benefit of the successors and permitted assigns of the parties. Any assignment not in accordance with this Agreement will be void.

15.2 Notices. Any notices required or permitted hereunder will be given to the appropriate party at the address specified below or at such other address as such party will

specify in writing. Such notice will be deemed given upon personal delivery, one day after the date such notice is provided by overnight delivery service, three days after the date of mailing when sent by certified or registered mail, postage prepaid, or upon the date such notice is transmitted by facsimile. All notices will be addressed as follows:

If to Bruker:
Bruker Daltonics Inc.
40 Manning Road
Billerica, MA 01821
Attention: Vice President of Finance
Facsimile: (978) 667-5993

With a copy to:
Bruker Daltonics Inc.
40 Manning Road
Billerica, MA 01821
Attention: John Wronka, Ph.D.
Facsimile: (978) 667-5993

If to Ibis:
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attention: Executive Vice President
Fax: (760) 268-4989

With a copy to:
Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attention: General Counsel
Fax: (760) 268-4922

With a copy to: Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008-7208
Attention: President, Ibis Biosciences division of Isis Pharmaceuticals, Inc.
Fax: (760) 603-4653

Either party may by like notice specify or change an address to which notices and communications will thereafter be sent.

15.3 Governing Law. This Agreement will be governed by and construed in accordance with the laws of the State of Delaware, without regard to conflicts of laws principles.

15.4 Relationship of the Parties. Nothing in this Agreement will constitute, nor will any party represent that there is any relationship of employer and employee, principal and agent, partnership, joint venture or agency of any kind between the parties as a result of this Agreement. Neither party 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 party, without the prior written consent of the other party.

15.5 Compliance with Laws. Ibis and Bruker each agree that it will comply with all applicable laws, rules and regulations in performing its obligations hereunder.

15.6 Severability. Any term or provision of this Agreement held to be illegal or unenforceable will, if possible, be interpreted so as to be construed as valid, but in any event the validity or enforceability of the remainder hereof will not be affected.

15.7 Waiver. Except as specifically provided for herein, the waiver from time to time by either party of any right or failure to exercise any remedy will not operate or be construed as a continuing waiver of the same right or remedy or of any other of such party's rights or remedies provided under this Agreement.

15.8 Headings. The section headings appearing in this Agreement are inserted only as a matter of convenience and in no way define, limit, construe or describe the scope or extent of such section.

15.9 Mutually Drafted Agreement. This Agreement has been negotiated by both parties and their counsel, and no presumption will be drawn against either party based on its drafting of any particular provision hereof.

15.10 Entire Agreement; Amendment. This Agreement (including its exhibits and schedules, which are incorporated by reference herein) sets forth all of the agreements and understandings between the parties hereto with respect to the subject matter hereof, and supersedes and terminates all prior agreements and understandings between the parties with respect to the subject matter hereof. There are no agreements or understandings with respect to the subject matter hereof, either oral or written, between the parties other than as set forth herein. Except as expressly set forth in this Agreement, no subsequent amendment, modification or addition to this Agreement will be binding upon the parties hereto unless reduced to writing and signed by the respective authorized officers of the parties.

15.11 Counterparts. This Agreement may be executed simultaneously in two or more counterparts, each of which will be considered an original, but all of which together will constitute one and the same instrument. A party may evidence its execution and delivery of this Agreement by signing and faxing this Agreement to the other party and promptly thereafter mailing the signed original copy of this Agreement to the other party.

15.12 Force Majeure. No party will be liable for any delay or failure of performance (other than payment obligations) to the extent such delay or failure is caused by circumstances beyond its reasonable control (including without limitation, fire, floods, earthquakes, natural disasters, embargoes, war, acts of war (whether war be declared or not), acts of terrorism, insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, acts of God or acts, omissions or delays in acting by any governmental authority or the other party) and that by the exercise of due diligence it is unable to prevent, provided that the party claiming excuse uses its commercially reasonable efforts to overcome the same.

15.13 U.S. Government Rights. Bruker acknowledges and agrees that certain Ibis Technology was developed in part with funds furnished by the U.S. Government and that the U.S. Government has certain rights relative thereto. This Agreement is explicitly made subject

to the U.S. Government's rights under any applicable law or regulation. To the extent that there is a conflict between any such applicable law or regulation and this Agreement, the terms of such applicable law or regulation will prevail.

[THIS SPACE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, the parties have caused this Manufacturing, Commercialization and Development Agreement to be executed by their duly authorized representatives as of the Effective Date.

ISIS PHARMACEUTICALS, INC. **BRUKER DALTONICS INC.**

By: /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: EVP & CFO

By: /s/ Frank H. Lavuien
Name: Frank H. Lavuien
Title: President

[COUNTERPART SIGNATURE PAGE TO MANUFACTURING, COMMERCIALIZATION AND DEVELOPMENT AGREEMENT]

Exhibit A

DEFINITIONS

"Affiliate" means a Person that, directly or indirectly, is controlled by Bruker or Ibis, as applicable; provided, however that, for Bruker, an Affiliate will include only entities that are controlled by Bruker BioSciences Corporation. For the purposes of this definition, the term "control" means the possession, directly or indirectly, of the power to govern the financial and the operating policies or to appoint the management of Bruker or Isis, as applicable.

"Calendar Quarter" means each respective period of three consecutive calendar months ending on March 31, June 30, September 30 and December 31.

"Confidential Information" means any confidential or proprietary information of a party, including, without limitation, any information relating to any research project, work in process, future development, scientific, engineering, manufacturing, marketing, business plan, financial or personnel matter relating to either party, its present or future products, sales, suppliers, customers, employees, investors or business, whether in oral, written, graphic or electronic form; provided, however, that such information is in writing and marked "confidential" (or with another similar designation) or, if disclosed orally, visually or through other non-written communication, such information is reduced to writing and so marked. Without limiting the generality of the foregoing, the parties agree that the Ibis Technology is Confidential Information of Ibis, the financial terms of this Agreement are Confidential Information of both parties and the MicrOTOF Technology is Confidential Information of Bruker.

"Effective Date" has the meaning provided in the opening clause.

"End User" means, with respect to Ibis Consumables or T5000 Systems, a Person who obtains such Ibis Consumables or T5000 System for its own use.

"European/Middle East Territory" means the following countries: Afghanistan, Albania, Andorra, Austria, Bahrain, Belarus, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Cyprus (including the Republic of Cyprus and the Republic of Northern Cyprus), Czech Republic, Denmark, Egypt, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Iran (presently not sold to), Iraq, Ireland, Israel, Italy, Jordan, Kuwait, Kyrgyzstan, Latvia, Lebanon, Liechtenstein, Lithuania, Luxembourg, Malta, Moldova, Monaco, Norway, Oman, Pakistan, Poland, Portugal, Qatar, Romania, Russia, San Marino, Saudi Arabia, Serbia and Montenegro, Slovakia, Slovenia, Spain, Sweden, Switzerland, Syria (presently not sold to), Tajikistan, The Netherlands, Turkey, Turkmenistan, Ukraine, United Arab Emirates, United Kingdom, Uzbekistan and Vatican City.

"Extended Warranty(ies)" has the meaning set forth in Exhibit B.

"Extended Warranty Revenues" means the gross receipts received by Bruker and its Affiliates for sales of Extended Warranties to End Users.

"**Extension Term**" has the meaning provided in Section 11.1.

"Government Use" means use primarily in connection with (a) defense, including homeland security, (b) food testing, (c) human forensics and (d) veterinary care and treatment by departments and agencies of national, state or local governments (or their respective contractors acting in their capacity as contractors to such entities) of countries comprising the European/Middle East Territory, but not including any IVD Use.

"Ibis" has the meaning provided in the opening clause.

"Ibis Amplicon Desalting Module" means an automated instrument for performing sample injection and clean-up procedures.

"Ibis Analytical Systems" means Ibis' proprietary analysis software and databases, as more fully described in Schedule 2, as updated from time to time by written agreement of the parties, as well as third-party software that is a part of the T5000 System.

"Ibis Consumables" means primers, reagent solutions and other consumables for use with the T5000 System, as more fully described in Schedule 1, as such may be amended from time to time by the parties.

"Ibis Partner" means any Third Party with whom Ibis has entered into an agreement for the sale and delivery of T5000 Systems.

"Ibis President" means the President of the Ibis Biosciences division of Isis Pharmaceuticals, Inc.

"Ibis Technology" means the Intellectual Property Rights owned or licensed by Ibis that are reasonably related to the T5000 System (including, without limitation, the patents and patent applications set forth on Schedule 4).

"Improvement" means any enhancement or modification (whether or not patentable) to the Ibis Technology or the Bruker Technology, as applicable, that is conceived or reduced to practice by either party or by the parties jointly during the Term or the Transition Term in the course of performing under this Agreement.

"Initial Period" means, with respect to a particular T5000 System, the 365 day period immediately following Installation of such T5000 System.

"Initial Term" has the meaning provided in Section 11.1.

"Installation" means unpacking and physically placing and securing a T5000 System at an End User's facility, making all necessary electrical and fluidic connections, installing the Ibis Analytical Systems on the T5000 System (to the extent not already installed), running diagnostic routines (to the extent not already performed at Bruker's facilities), making necessary adjustments and demonstrating to appropriate personnel of the End User that, upon completion of the foregoing activities, the T5000 System functions in accordance with the customer acceptance specifications found in Schedule 3. "Install," "Installed" and related terms will have correlative meanings.

"Intellectual Property Rights" means any and all Patent Rights, business processes, data rights, copyrights, moral rights, trade names, trademarks, mask works, trade secrets, know-how, knowledge, techniques, technology, practices, methods, test data and results, analytical and quality control data, results or descriptions, software and algorithms and other intellectual property rights, whether registered or unregistered, arising or enforceable under United States law or the law of any other jurisdiction or international treaty regime.

"Invention" means any invention or discovery, whether or not patentable, that is conceived or reduced to practice by either party or by the parties jointly in the course of performing under this Agreement.

"IVD Use" means use primarily in connection with (a) human *in vitro* diagnostics and (b) "homebrew" applications, including "analyte specific reagent" (ASR) use under the Clinical Laboratory Improvement Act of 1988 (CLIA) and comparable legislation and regulations in other jurisdictions.

"Marks" means, as to each party, those trademarks, trade names and logos set forth under such party's name on Schedule 5, as such may be amended from time to time by the parties.

"MicrOTOF" means Bruker's mass spectrometer (not including the FOCUS™ option), as more fully described in Schedule 6, as updated from time to time by written agreement of the parties.

"MicrOTOF II" means a second-generalation MicrOTOF that incorporates Bruker's Apollo II Dual Ion Funnel Source and is designed to be compatible for use with T5000 Systems developed for Regulated Uses (including uses in connection with the diagnosis or treatment of humans or animals).

MicrOTOF Technology" means the Intellectual Property Rights owned or licensed by Bruker or any of its Affiliates that are reasonably related to the MicrOTOF (including, without limitation, the patents and patent applications set forth on Schedule 7).

"Non-Exclusive Market" means that market consisting of End Users located in the European/Middle East Territory using Ibis Systems for Other Use.

"North American Territory" means Canada, Mexico and the United States and its territories and possessions.

"Other Use" means any use other than Government Use and IVD Use.

"Partnering Transaction" means an agreement providing a Third Party with the right, among other things, to promote, sell and supply T5000 Systems and/or Ibis Consumables in the European/Middle East Territory other than an agreement relating solely to IVD Use.

"Patent Rights" means all rights associated with United States and foreign patents (including all reissues, extensions, confirmations, registrations, re-examinations, and inventor's

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certificates) and patent applications (including, without limitation, all substitutions, continuations, continuations-in-part, provisionals and divisionals thereof).

"Person" means any corporation, natural person, firm, joint venture, partnership, trust, unincorporated organization, government or any department or agency of such government.

"Renewal Update(s)" means Updates that Ibis may, from time to time, develop and make generally available to the public after the Initial Period.

"Specifications" means the specifications to be prepared and approved by the parties prior to the Technology Transfer Date.

"System Revenues" means the amounts invoiced, or reflected in purchase orders received, by Bruker and its Affiliates for sales of T5000 Systems to End Users, less (a) transportation, customs, duties, delivery and similar charges, including insurance premiums, actually incurred by Bruker or its Affiliates or paid by an End User and reimbursed by Bruker and (b) taxes (other than franchise or income taxes on the income of Bruker or its Affiliates) actually paid by or withheld from Bruker or its Affiliates or paid by an End User and reimbursed by Bruker, provided that upon the refund of any such tax or reimbursement to Bruker, such refund or reimbursement will be included in the amount invoiced or the purchase order received.

"T5000 Systems" means the fully integrated system comprising a MicrOTOF, an Ibis Amplicon Desalting Module, the Ibis Analytical Systems and other computers and hardware, as more fully described in Schedule 3, as updated from time to time by written agreement of the parties. "T5000 Systems" does not include Ibis Consumables. "T5000 Systems" includes new versions of the T5000 System as it exists as of the Effective Date, as well as successor products designed to perform mass spectrometry analysis of PCR products, but excluding any systems exclusively used for IVD Use.

"Technology Transfer Date" has the meaning provided in Section 2.2.

"Technology Transfer Management Committee" or **"TMC"** means the committee described in Article 2.

"Term" means the Initial Term and the Extension Terms, if any.

"Third Party" means an entity other than Ibis, Bruker and their respective Affiliates.

"Transition Term" has the meaning provided in Section 11.2.

"Updates" means modifications, corrections, fixes, patches, enhancements, updates, upgrades or extensions to the Ibis Analytical Systems that Ibis may, from time to time, develop and make generally available to the public during the Initial Period.

"U.S. Government" means the federal, state and local governments of the U.S. or any regulatory authority or department, agency, branch, arm or similar division (including procurement arms) of such governments.

Exhibits and Schedules

Exhibit A	Definitions
Exhibit B	Commercialization Plan
Exhibit C	Press Release
Exhibit D	Bruker Terms and Conditions
Schedule 1	Ibis Consumables
Schedule 2	Ibis Analytical Systems (including Ibis databases)
Schedule 3	T5000 System
Schedule 4	Ibis Technology
Schedule 5	Marks
Schedule 6	MicrOTOF
Schedule 7	MicrOTOF Technology

Exhibit B

Commercialization Plan

[***]

Exhibit C

Press Release

[***]

Exhibit D

Bruker Terms and Conditions

[***]

Schedule 1

Ibis Consumables

[***]

Schedule 2

Ibis Analytical Systems (including Ibis databases)

[***]

Schedule 3

T5000 System

[***]

Schedule 4

Ibis Technology

[***]

Schedule 5

Marks

[***]

Schedule 6

MicrOTOF

[***]

Schedule 7

MicrOTOF Technology

[***]

EXHIBIT 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

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

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

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

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

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

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Dated: November 7, 2006

/s/ Stanley T. Crooke

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

EXHIBIT 31.2

CERTIFICATION

I, B. Lynne Parshall, certify that:

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

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

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

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

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

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

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

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

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

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

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

Dated: November 7, 2006

/s/ B. Lynne Parshall

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

Exhibit 32.1

CERTIFICATION

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

1. The Company's Quarterly Report on Form 10-Q for the period ended September 30, 2006, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: November 7, 2006

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

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