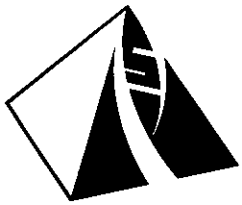
2006
ANNUAL REPORT



ISIS®
PHARMACEUTICALS

Dear Fellow Stockholders,

2006 was a great year for Isis, and we are pleased that stockholders began to see the value we are building reflected in our share price. Yet we believe that we are just beginning to achieve the recognition and command the value that our technology and pipeline warrant. In 2006 we reported exciting Phase 2 data for our key asset and lead cardiovascular drug, ISIS 301012, showing that it can significantly lower all atherogenic lipids. ISIS 113715, our lead diabetes drug, demonstrated significant reduction in both glucose and cholesterol in the first Phase 2 study for this drug. Our partners made important progress on many fronts, including advancing four anti-cancer drugs in development. Underscoring our technology leadership, we continued to add new inventions to our extensive patent estate that spans the breadth of RNA-based drug mechanisms, structures and medicinal chemistry. We also advanced our Ibis biosensor business into commercialization. Finally, we strengthened our balance sheet significantly, and we now have ample resources to continue moving our drugs toward the market.

We Are Pioneers

Since inception we have been innovators developing a new class of drugs based on targeting RNA. We have built a powerful drug-discovery platform, and we continue to expand our knowledge base and experience, protecting our inventions along the way. Along with optimized chemistry, our second-generation antisense approach includes strategic elements that guide our selection of targets and diseases. We choose targets in tissues where our drugs distribute most effectively and we choose diseases for which we can measure drug activity unambiguously in early-stage testing. As a result, we and our partners have reported multiple examples of drugs with clear activity in Phase 2 testing. Further, our inventions surrounding RNA antisense mechanisms and oligonucleotide chemistry serve as a foundation for early-stage drugs that exploit other antisense mechanisms including the emerging siRNA and microRNA therapeutic fields. We are advancing these technologies in our own labs and in partnerships with industry leaders.

The Power of Our Platform

Now that we've created and validated our antisense technology platform, we believe that we can discover better drugs more rapidly than other drug discovery methods. In contrast to traditional small molecule approaches, antisense technology allows us to create a drug for virtually any target formulaically based on gene sequence with exquisite specificity. High specificity means that antisense drugs may be less toxic than traditional drugs because we can design them to minimize the impact on unintended targets. Since antisense drugs share chemical "class" properties, we can largely predict how a new antisense drug will behave and we can evaluate the strengths and limitations of prospective drug candidates before moving them forward into later stage development. This predictable behavior underpins the efficiency of our drug discovery efforts, giving us the power to keep our pipeline full of promising therapeutic opportunities.

Our cardiovascular and metabolic disease programs epitomize our approach. Both programs are relatively new. Both involved evaluation of scores of potential targets, including many "undruggable" targets. And both programs have very quickly produced exciting development pipelines with the first drugs already in Phase 2 clinical trials.

Our Business Strategy

Our expertise is in RNA-based drug discovery and development. Our strategy is to out-license our drugs at value inflection points and build a growing annuity of milestone and royalty income. By doing this, we can leverage our partners' existing drug development resources before launch, and then benefit from their sales and marketing infrastructures to commercialize our drugs. We do not intend to market or sell drugs ourselves.

With the pioneering work we have done in developing our technology platform, we can discover and validate many more drug candidates than we can advance ourselves. For key therapeutic areas, including cardiovascular and metabolic diseases, we internally develop our drugs to a point where we believe we have established significant value. We license drugs that fall outside our strategic therapeutic areas at earlier stages to partners with disease-area expertise. This practice has led to our expansive external pipeline, which currently numbers 11 drugs. We now have a total of 17 drugs in our development pipeline, a remarkable achievement for a company our size. Our strategy is sound. More importantly, we are executing it successfully.

Strategy Execution

Within Isis' rich pipeline are several growing therapeutic programs. We focus internal development efforts primarily on our cardiovascular and metabolic disease drugs, while our partners are developing drugs for other indications, including cancer and inflammatory diseases.

Leading our cardiovascular program, ISIS 301012 is a key asset. ISIS 301012 has demonstrated the feasibility of systemically delivered antisense drugs. Equally important, it has demonstrated significant activity, reducing harmful forms of cholesterol in patients both when dosed as a single agent and when added to statins. We have dosed nearly 200 patients and the drug has been well tolerated, even in patients on very high doses of statins and ezetimibe. Our six-month and twelve-month monkey and six-month mouse chronic toxicology studies are complete and continue to support the safety profile even at the high doses given in those studies. We are looking forward to initiating longer-term human studies this year. We're also looking forward to beginning our registration study for familial hypercholesterolemia in the same time frame. We believe that familial hypercholesterolemia represents the most rapid path to commercialization of ISIS 301012. We've expanded our cardiovascular pipeline with the addition of an antisense drug targeting C-reactive protein (CRP) in preclinical development and a new candidate targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) now in late-stage discovery.

We're also very enthusiastic about our metabolic disease program. Our PTP-1b antisense inhibitor, ISIS 113715, is our lead diabetes drug in Phase 2 studies, followed by ISIS 325568, targeting glucagon receptor, which we expect to advance into Phase 1 in 2007. We recently started preclinical development of our third diabetes drug, ISIS 377131, targeting glucocorticoid receptor. In 2006, we reported data from a trial of ISIS 113715 in treatment-naïve patients recently diagnosed with type 2 diabetes. ISIS 113715 significantly reduced glucose levels and cholesterol. The single-agent treatment was well tolerated in all dose cohorts, and we are continuing development in an important Phase 2 study adding ISIS 113715 in patients who are not achieving adequate control of their disease with sulfonylureas (routine oral anti-diabetic treatment). Because ISIS 113715 is an insulin sensitizer that acts by increasing the activity of the insulin receptor in response to insulin, the most logical place for this drug in the diabetes treatment regimen is as an adjunct to insulin therapy, and that's how we initially plan to develop this drug for registration.

In the hands of our partners, our pipeline for cancer, and inflammatory and other diseases continued to grow and mature in 2006. Our partners OncoGenex and Lilly each advanced two Isis anti-cancer drugs in development. We are pleased that many of our partners, having licensed an initial antisense drug and begun development, have subsequently taken licenses to expand their own pipelines with additional antisense candidates for further targets. Our partnering strategy enables more Isis drugs to advance into clinical development, adding to the cumulative experience with antisense drugs and providing present and future revenue to us through milestones, royalties and frequently, in the

case of satellite companies, equity ownership in the partner companies.

Ibis Biosciences

The Ibis T5000™ Biosensor System represents another important extension of our technology. Ibis technology applies PCR, mass spectrometry and computational analysis to create a completely new and powerfully versatile approach for determining the presence and nature of biological organisms in a sample without prior knowledge of what might be present. We believe the Ibis T5000 Biosensor System has the potential to transform the fields of forensics, epidemiology and eventually, diagnostics.

Financing Success

In 2006, we completed important financings with Symphony Capital and with Azimuth Opportunity Ltd. Together, these two partners enabled us to add to our balance sheet with $150 million in cash on attractive terms. In January, we completed an extremely successful private placement of convertible debt that will enable us to retire and replace existing debt with lower-cost, longer-maturity notes, saving over $2.5 million per year in interest expense. These financing activities significantly strengthened our balance sheet and, based on reasonable assumptions for new sources of revenue and cash, we believe we have sufficient resources to meet our anticipated funding requirements through at least the middle of 2010.

Looking Ahead

With our growing and maturing pipeline, we are evolving as a company. We continue to execute our corporate strategies, strengthen our balance sheet, and invest in our key therapeutic areas while participating in the fruits of our inventions outside our areas of focus through partnerships. We have an exceptional management team, most recently bolstered by the addition of Dr. Jeffrey Jonas, who joined Isis as Executive Vice President. Jeff brings valuable drug development experience to Isis at a time when our rich pipeline is progressing rapidly, and we're thrilled to have him as part of our executive leadership team.

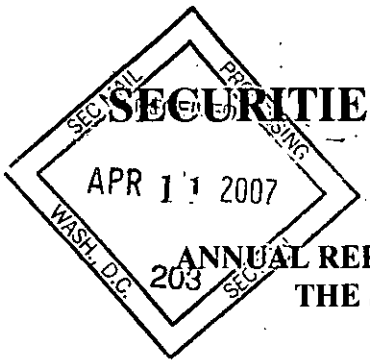
In 2007, we will continue to execute on our strategy. We plan to advance our cardiovascular and metabolic development pipeline. We're also hopeful that the drugs in our partnered pipeline will continue to advance in multiple disease areas. And we expect our Ibis subsidiary to place at least eight systems in its first full year of commercial sales.

As the market continues to more fully understand our discovery platform, our therapeutic programs and key assets, our partnered pipeline and our Ibis business, we hope the investment community will begin to revise its Isis valuation to more adequately reflect the sum of increasingly attractive parts.

We look forward to sharing our progress with you as 2007 unfolds.

Thank you for your ongoing support,

Stanley T. Crooke, M.D., Ph.D.



UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-K

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

For the fiscal year ended December 31, 2006

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 is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark whether the Registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the Registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☐ Accelerated filer ☒ Non-accelerated filer ☐

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The approximate aggregate market value of the voting common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on the NASDAQ Global Market was $370,713,357 as of June 30, 2006.*

The number of shares of voting common stock outstanding as of March 5, 2007 was 82,484,960.

DOCUMENTS INCORPORATED BY REFERENCE

(To the extent indicated herein)

Portions of the Registrant's definitive Proxy Statement for the fiscal year ended December 31, 2006 to be filed on or about April 5, 2007 with the Securities and Exchange Commission in connection with the Registrant's annual meeting of stockholders to be held on May 17, 2007 are incorporated by reference into Part III of this Report. The Exhibit Index (Item No. 15) located on pages 83 to 88 incorporates several documents by reference as indicated therein.

* Excludes 11,628,302 shares of common stock held by directors and officers and by stockholders whose beneficial ownership is known by the Registrant to exceed 10% of the common stock outstanding at June 30, 2006. Exclusion of shares held by any person should not be construed to indicate that such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the Registrant, or that such person is controlled by or under common control with the Registrant.

FORWARD-LOOKING STATEMENTS

This report on Form 10-K and the information incorporated herein by reference contains forward looking statements regarding our business, the financial position of Isis Pharmaceuticals, Inc., including Ibis Biosciences, Inc., and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, financial or other projections, 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 and projections. 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 drugs and 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. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this report on Form 10-K, including those identified in Item 1A entitled "Risk Factors". 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.

TRADEMARKS

Affinitak™ is a trademark of Eli Lilly and Company.

Macugen® is a registered trademark of (OSI) Eyetech, Inc.

Ibis Biosciences™ is a trademark of Isis Pharmaceuticals, Inc.

Ibis T5000™ is a trademark of Isis Pharmaceuticals, Inc.

Vitravene® is a registered trademark of Novartis AG.

Isis Pharmaceuticals® is a registered trademark of Isis Pharmaceuticals, Inc.

CORPORATE INFORMATION

We incorporated in California in 1989, and in January 1991 we changed our state of incorporation to Delaware. Our principal offices are in Carlsbad, California. We make available, free of charge, on our website, *www.isispharm.com*, our reports on forms 10-K, 10-Q, 8-K and amendments thereto, as soon as reasonably practical after we file such materials with the Securities and Exchange Commission. Any information that is included on or linked to our Internet site is not a part of this report or any registration statement that incorporates this report by reference. Our filings may also be read and copied at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. Information on the operation of the Public Reference Room may be obtained by calling the SEC at 1-800-732-0330. The SEC also maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that site is *www.sec.gov*.

PART I

ITEM 1. Business

Overview

We are a biopharmaceutical company exploiting proprietary RNA-based drug discovery technologies to create a new class of drugs to treat important diseases. RNA, or ribonucleic acid, is a molecule that provides to a cell the information the cell needs to produce proteins, including those proteins associated with disease. Interference with RNA can keep the body from producing the proteins that are involved in disease. We are the leader in making drugs that target RNA, and have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors, called oligonucleotides, designed to hybridize, with a high degree of specificity to their RNA target and modulate the production of specific proteins associated with disease. Separately, within our Ibis Biosciences subsidiary, we have developed a revolutionary biosensor system, called the Ibis T5000 Biosensor System, that can simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample.

Over the past 18 years, we have built a business dedicated to RNA-based drug discovery and development. This is our expertise, and we are fostering the innovations that enable creation of this entirely new class of drugs—antisense drugs. We successfully developed the first marketed antisense drug, Vitravene®. The regulatory approval we received for Vitravene demonstrated our ability to meet Food and Drug Administration (FDA), and European regulatory requirements for safety and efficacy, and for the commercial manufacture of antisense drugs. With the pioneering work we have done in developing our technology platform, we can discover and validate many more drug candidates than we can advance ourselves. Our strategy is to apply our expertise to discover and develop drugs, advancing them to strategic points and then to license them to others to leverage their resources and existing infrastructures. Our key therapeutic areas are cardiovascular and metabolic diseases, and we develop drugs in these franchises internally to points where we believe we have established significant value before partnering them. In other therapeutic areas, our strategy is to work with partners sooner in the discovery and development process to take advantage of their therapeutic area of focus to build on our development pipeline. The strategy is working. It has allowed us to maintain internal focus while creating an expansive pipeline with multiple partnership franchises in cancer, inflammation, ocular, and other disease areas. We and our partners currently have 17 drugs in development, many of which are in Phase 1 or Phase 2 human clinical trials. Our pipeline has matured to consist almost entirely of drugs based on our proprietary second generation chemistry. Our second generation antisense drugs have the potential to be safer and more effective than our first generation drugs. In addition, because second generation drugs have a longer half-life, they have the potential to produce long-duration of therapeutic response and to support more convenient, less-frequent dosing.

Additionally, over the last seven years, within Ibis, we have developed the Ibis T5000 Biosensor System, a biosensor system that has the potential to revolutionize the identification of infectious organisms. Supported by substantial government funding, Ibis has developed a system that can rapidly identify infectious organisms in a sample without prior knowledge of what may be in the sample. We are commercializing the Ibis T5000 Biosensor System for use in biodefense, forensics, epidemiological surveillance, infectious disease research, hospital-associated infection control and plan to commercialize the Ibis T5000 Biosensor System for *in vitro* diagnostics, or IVD.

We have continued to protect our substantial innovation and investment in RNA-based technologies and products. With more than 1,500 issued patents, we remain one of the largest patent holders in the U.S. With our ongoing research and development this patent portfolio continues to grow. The patents not only protect our key assets—our technology, our drugs, and the Ibis T5000 Biosensor System—they also form the basis for lucrative licensing and partnering arrangements.

In the past year, we and our partners made important progress on all of our drugs in development. Also in 2006, Ibis reached a key milestone as it began commercializing the Ibis T5000 Biosensor System. We also took important steps to strengthen our balance sheet and our organization. Below is a list of some of our key accomplishments for 2006 and early 2007.

2006 and Early 2007 Business Highlights

Cardiovascular Program

The leading drug in our cardiovascular program is ISIS 301012, a drug that inhibits production of apoB-100 to treat high cholesterol by lowering low-density lipoproteins, or LDL, and other harmful lipids. We are developing ISIS 301012 to help the significant and growing number of patients who are unable to achieve recommended LDL levels with available lipid lowering therapies such as statins. Phase 2 development of ISIS 301012 is continuing in multiple studies.

- In November 2006, at the American Heart Association meeting, we reported Phase 2 results from two studies: a monotherapy study and an add-on study with statins. Patients in both of these studies experienced potent, linear, dose-dependent reductions in all harmful lipids and triglycerides, and these reductions were comparable when ISIS 301012 was administered as a single agent or when it was added to ongoing statin therapy. ISIS 301012 was well tolerated in these studies. We are looking at higher dose groups in both studies as well as longer dosing in the add-on study.
- We secured $75 million of financing from Symphony Capital to fund development of ISIS 301012 through the completion of registration-supporting clinical studies in patients with familial hypercholesterolemia and through the completion of Phase 2b development in routine high cholesterol patients as well as to develop through proof-of-concept clinical trials two new metabolic disease drugs. Consistent with our strategy, these funds will enable us to fund and control the development of ISIS 301012 to key value inflection points prior to partnering.

Metabolic Program

We made progress with our metabolic disease program in 2006, and with funding from Symphony Capital, we now have three diabetes drugs in development, each with distinct potential profiles.

- We reported positive Phase 2 results for ISIS 113715, which inhibits production of PTP-1b. In the single-agent, dose-escalation study in treatment-naïve patients with type 2 diabetes, we reported at the American Diabetes Association 2006 Scientific Sessions that ISIS 113715 reduced glucose levels, and also lowered cholesterol. In this small, short-term study we did not see a statistically significant improvement in glycosylated hemoglobin, or HbA1c, which is a measure of long-term glucose control. The single-agent treatment was well tolerated in all dose cohorts. We are continuing development of ISIS 113715 in a combination study treating patients with type 2 diabetes whose disease is not adequately controlled with sulfonylureas, a class of commonly used oral antidiabetics.
- We also advanced the first of two new metabolic disease program drugs funded by Symphony Capital, ISIS 325568, into toxicology and pharmacokinetic studies in animals to support the initiation of human clinical studies. ISIS 325568 targets the receptor for glucagon, or GCGR, which is a hormone that opposes the action of insulin and stimulates the liver to produce glucose. Reducing the expression of GCGR using antisense drugs, and thereby reducing excessive liver glucose production, should lower blood sugar and help control type 2 diabetes.
- We recently advanced the second new diabetes drug funded by Symphony Capital, ISIS 377131, targeting the glucocorticoid receptor, or GCCR, into our development pipeline. Glucocorticoids promote breakdown of protein and fat from storage and ultimately result in increased liver glucose

production. Reducing GCCR levels should reduce glucocorticoid action and have a beneficial effect on glucose control, blood lipid levels and body fat.

Partner Development Pipeline

Our partnered pipeline continued to grow and mature in 2006, enabling us to advance more drugs into clinical development, adding to the cumulative experience with antisense drugs and providing present and the potential for future revenue to us through milestones, royalties and in the case of satellite companies, equity participation in the partner companies. In 2006, activities of our partners in oncology, Eli Lilly and Company and OncoGenex Technologies Inc., exemplified the valuable pipeline expansion enabled by our partnering strategy.

- OncoGenex showed encouraging Phase 1 activity in patients with non-small cell lung cancer for OGX-011, an antisense inhibitor of clusterin now in five Phase 2 trials. We are co-developing this drug with OncoGenex, which has a second antisense drug, OGX-427, targeting Hsp27, that it expects to begin testing in Phase 1 clinical trials in 2007.
- Lilly highlighted two of our cancer drugs in its pipeline: LY2181308, targeting survivin, is poised to enter a broad Phase 2 program in 2007, and LY2275796, targeting eIF-4E, continues in Phase 1.

Intellectual Property, Licensing and Partnering Activity

With over 1,500 issued patents, we continue to protect our inventions as a pioneer in RNA-based drug discovery. We had several notable achievements related to our technology platform.

Awarded Key Patents

- We were awarded several key U.S. patents, including a patent protecting our antisense drugs with modified sugars until 2023, a patent that broadly covers certain chemical modifications of oligonucleotides and the first issued patent protecting our core Ibis business. Additionally, the European Patent Office upheld on appeal a key Isis patent covering antisense drugs with gapmer structures.

Added Four New Satellite Companies

- We licensed our aminoglycoside antibiotics program to Achaogen, Inc.
- We licensed an aptamer drug, ISIS 5320, to ImQuest Pharmaceuticals, Inc. to be developed as an anti-HIV topical microbicide.
- We and Rosetta Genomics Ltd. entered into a research collaboration to discover and develop antisense drugs that regulate microRNAs.
- We licensed alicaforsen to Atlantic Healthcare Limited for further development.

Generated More Than $10 Million From Licensing Activities

- We received a $1 million milestone payment from Merck & Co., Inc. for the initiation of clinical trials of a compound that was discovered during a research collaboration between the companies.
- Alnylam Pharmceuticals, Inc. paid us $750,000 related to its sublicense of our technology to a pharmaceutical company.
- We received $8 million from Drug Royalty USA, Inc. related to Macugen.

- We received a milestone payment from iCo Therapeutics Inc. based on its filing of an Investigational New Drug, or IND, application for iCo-007.
- We and Pfizer Inc. extended our research agreement, adding to the scope of target validation activities.

Ibis Biosciences, Inc.

2006 marked the transition of Ibis Biosciences from research and development to initial commercialization. Reflecting this maturation, we have reorganized the division to be a wholly owned subsidiary called Ibis Biosciences, Inc.

- Ibis announced a strategic alliance with Bruker Daltonics Inc., a subsidiary of Bruker Biosciences Corporation. Bruker Daltonics will provide Ibis T5000 instrument manufacturing along with global installation and support services.
- Ibis earned revenue from its first commercial orders for Ibis T5000 Biosensor Systems and assay services.

Financing Activity

In 2006 and early 2007, we completed three important transactions that significantly strengthened our balance sheet.

- We received $75 million from our collaboration with Symphony GenIsis to fund continued development of ISIS 301012 and two preclinical metabolic disease program drugs targeting GCGR and GCCR.
- We raised $75 million by selling approximately 8.0 million shares of our common stock at an average price of $9.41 per share under our equity line of credit with Azimuth Opportunity Ltd.
- In early 2007, we issued lower-coupon (2⅛%) longer-maturity (due 2027) convertible notes, the proceeds of which we intend to use to repurchase our existing 5 ½% convertible subordinated notes due 2009. We expect to save approximately $2.6 million per year in interest payments as a result of this transaction, and the extended maturity further strengthens our balance sheet.

Drug Discovery and Development

Antisense Drug Discovery

Proteins are essential working molecules in a cell. Almost all human diseases result from inappropriate protein production or improper protein activity. Scientists use traditional drug discovery methods to design drugs to interact with the proteins in the body, proteins that are supporting or causing a disease. Antisense drugs are different from traditional small molecule drugs because they interrupt the production of disease-causing proteins. We design our antisense drugs, or antisense inhibitors, to act earlier in the disease process than traditional drugs and to interrupt the production of disease-causing proteins without disrupting other proteins responsible for the body's normal functions.

Genes contain the information necessary to produce proteins. A gene is made up of nucleoside bases: Adenine, Thymine, Guanine, and Cytosine, commonly known as A, T, G and C, which are linked together to form a two-stranded structure that resembles a twisted ladder, known as deoxyribonucleic acid, or DNA. The nucleotides on one side of the ladder bind weakly to complementary nucleotides on the other strand according to specific rules; for example, A pairs with T and G pairs with C, creating the ladder's rungs. This highly specific nucleotide pairing is called hybridization. The sequence or order of these nucleotides establishes the cell's recipes for making proteins. Each protein's instructions reside in a corresponding segment of DNA known as a gene.

When a cell transcribes information from DNA gene into messenger RNA, or mRNA, the two complementary strands of the DNA partly uncoil. One strand acts as a template and information stored in the DNA strand is copied into a complementary mRNA. mRNA then carries the information to cellular structures called ribosomes, the cell's factories for manufacturing proteins. The ribosome reads the encoded information, the mRNA's nucleotide sequence, and in so doing, strings together amino acids to form a specific protein. This process is called translation. Antisense technology interrupts the cell's protein production process by preventing the RNA instructions from reaching the ribosome, thus inhibiting the production of the protein. The mRNA sequence of nucleotides that carries the information for protein production is called the "sense" strand. The complementary nucleotide chain that binds specifically to the sense strand is called the "antisense" strand. We use the information contained in mRNA to design chemical structures, called antisense oligonucleotides or antisense drugs, which resemble DNA and RNA and are the complement of mRNA. These potent antisense drugs inhibit the production of disease-causing proteins. Antisense drugs can selectively inhibit one protein among a closely related group of proteins because antisense drugs interact with a specific gene RNA and not with the RNAs of other members of the group. It is easier to differentiate between closely related proteins at the RNA sequence level than by binding to the protein itself, as traditional drugs do. As a result, we can design antisense drugs that selectively inhibit the disease-causing member of the group without interfering with those members of the group necessary for normal bodily functions. This unique specificity means that antisense drugs may be less toxic than traditional drugs because we can design them to minimize the impact on unintended targets.

Further, the design of antisense compounds is less complex, more rapid and more efficient than traditional drug design directed at protein targets. Traditional drug design requires companies to identify a small molecule that will interact with protein structures to affect the disease-causing process. Since predicting which small molecules will do this has proven to be difficult, traditional drug discovery involves testing hundreds of thousands of small molecules for their ability to interfere with protein function. As a result, traditional drug discovery is a labor intensive, low probability endeavor. In contrast, we design our antisense compounds to bind to mRNA through well understood processes. We can design prototype antisense drugs as soon as we identify the sequence for the target mRNA. With the completion of the human genome sequencing project, we now know the sequence for all potential mRNA targets in the human body.

We are the leader in the discovery and development of this exciting new class of therapeutic compounds. Our proprietary technology to discover and characterize novel antisense inhibitors has enabled our scientists to modify the properties of our antisense drugs for optimal use with particular targets and thus, to produce a broad proprietary portfolio of compounds applicable to many disease targets. Further, over the past decade, our scientists have made great advances in chemistries, which we call our second generation antisense drugs. Second generation, including generation 2.2, antisense drugs may have increased potency, stability, oral bioavailability and an improved side effect profile. Our scientists have utilized our chemistry advancements to develop new formulations that expand the therapeutic and commercial opportunities of our pipeline.

Approved Product and Drugs In Development

We successfully developed the first antisense drug to reach the market, Vitravene, for CMV retinitis. Our partner, Novartis Ophthalmics AG, has exclusive worldwide distribution rights.

We have designed our drugs in development to treat a variety of health conditions, including cardiovascular, metabolic, inflammatory, ocular and neurodegenerative diseases, and cancer, and we and our partners are studying them in a variety of formulations both systemically and locally delivered. The following table lists our approved product and each of our and our partners' drugs in development, their targets, disease indications and the development status of each.

Our Drugs in Development

Product (1)	Target	Potential Disease Indication(s)	Partner	Preclinical (2)	Phase 1	Phase 2	Phase 3	Approved
CARDIOVASCULAR DISEASES								
ISIS 301012 (SC)	apoB-100	High Cholesterol	Isis (3)					
ISIS 353512 (SC)	CRP	Coronary Artery Disease	Isis					
METABOLIC DISEASES								
ISIS 113715 (SC)	PTP-1B	Diabetes	Isis					
ISIS 325568 (SC)	GCGR	Diabetes	Isis(3)					
ISIS 377131 (SC)	GCCR	Diabetes	Isis(3)					
INFLAMMATORY DISEASES								
ISIS 369645 (A)	IL-4R-α	Asthma/Rhinitis	Isis					

Our Partners' Drugs in Development

Product (1)	Target	Potential Disease Indication(s)	Partner	Preclinical (2)	Phase 1	Phase 2	Phase 3	Approved
CANCER								
OGX-011 (IV)	Clusterin	Cancer	OncoGenex					
LY2181308 (IV)	Survivin	Cancer	Lilly					
LY2275796 (IV)	eIF-4E	Cancer	Lilly					
OGX-427 (IV)	Hsp27	Cancer	OncoGenex					
INFLAMMATORY DISEASES								
Alicaforsen (ISIS 2302) (E)	ICAM-1	Ulcerative Colitis	Atlantic					
ATL1102 (SC)	VLA-4	MS	ATL					
OTHER DISEASES								
Vitravene® (I)	CMV	CMV Retinitis	Novartis (4)					
Merck Drug (T)	HCV	HCV Infection	Merck					
iCo 007 (I)	C-Raf kinase	Ocular Diseases	iCo					
ISIS 333611 (IT)	SOD1	ALS	ALSA (5)					
ISIS 5320 (T)	HIV	AIDS	ImQuest					
ATL1103 (SC)	GHr	Acromegaly	ATL					

(1) A = Aerosol; E = Enema; I = Intravitreal; IT = Intrathecal Infusion; IV = Intravenous; SC = Subcutaneous; T = Topical

(2) When we make a decision to test a drug in human clinical studies, it enters preclinical development. To file an IND (or foreign equivalent) and initiate such clinical studies, we must first conduct toxicology and pharmacokinetic studies, which we call IND-enabling studies, in animals.

(3) Part of our Symphony GenIsis Collaboration.

(4) Novartis has the exclusive worldwide rights to distribute Vitravene but no longer markets it.

(5) The ALS Association, or ALSA, is funding preclinical studies of ISIS 333611.

The following section provides more detailed descriptions of our approved product and those drugs in development and the disease indications they target. We also have a significant research program.

Our Drugs in Development

Cardiovascular Disease

Cardiovascular disease is the leading cause of death in the United States. Its underlying cause is atherosclerosis, or hardening of the arteries, that occurs when cholesterol and inflammatory cells accumulate in blood vessels. Researchers have shown a strong correlation between high cholesterol levels and subsequent cardiovascular diseases. Lowering cholesterol is a key component in the prevention and management of cardiovascular disease. Another independent risk factor for cardiovascular disease is high levels of C-reactive protein, or CRP, which are associated with significantly worse outcomes in patients with cardiovascular disease.

ISIS 301012 — ISIS 301012 reduces the production of apolipoprotein B-100, or apoB-100, which is the protein that carries certain forms of cholesterol and triglyceride particles in the bloodstream. Cholesterol can be carried in the bloodstream in a variety of forms, with high-density lipoprotein, or HDL, being the good form, and low-density lipoproteins or LDL, and very low-density lipoproteins, or VLDL, being the bad or atherogenic forms, which are directly involved in heart disease. ApoB-100 is a target that the pharmaceutical industry has long recognized as attractive for intervention but that has proved to be undruggable using traditional small molecule approaches.

We are developing ISIS 301012 as a new treatment for high cholesterol. We plan to develop ISIS 301012 for patients who are unable to achieve target cholesterol levels with statins alone, as well as for patients who are intolerant of statins. This is a large market opportunity. The current recommendations from the National Cholesterol Education Program's Adult Treatment Panel III are for LDL-cholesterol goals of less than 100 mg/dL for High Risk patients and less than 130 mg/dL for Moderately High Risk patients. Further reductions to these LDL targets have been proposed, and less than 70 mg/dL and 100 mg/dL are the optional targets for the High Risk and Moderately High Risk groups, respectively. Roughly 80% of the 20 million people in the U.S. in the High Risk category (or 16 million people in the U.S.) are not meeting LDL targets on their current lipid-lowering therapies, and 5 million of the more than 10 million Moderately High Risk patients are not achieving target levels taking statins. In other words, more than 20 million patients in the U.S. are in need of additional therapies to complement current lipid lowering drugs including statins.

We are also developing ISIS 301012 for patients with familial hypercholesterolemia, or FH, a genetic disorder that causes extremely high cholesterol levels—often exceeding 500 mg/dL—and results in the early onset of heart disease. The FDA granted ISIS 301012 Orphan Drug Designation for treatment of patients with homozygous FH, providing a potentially accelerated pathway to commercialization because of the unmet need in this very high risk patient population.

We are conducting Phase 2 trials in patients with FH in preparation for initiating later this year pivotal studies to support filing with the FDA for approval of ISIS 301012 for these patients. In parallel, we are

conducting Phase 2 trials to address the large commercial market represented by the traditional population of patients with high cholesterol who are not reaching their target cholesterol levels.

In November 2006, we reported positive results from two Phase 2 studies of ISIS 301012. In a Phase 2 study of ISIS 301012 as a single agent in patients with high cholesterol, ISIS 301012 produced rapid, prolonged dose-dependent reductions in apoB-100, LDL, and other atherogenic lipids. At a dose of 300 mg/week for three months, ISIS 301012 reduced LDL and triglycerides of 62% and 43%, respectively. In another Phase 2 clinical trial, patients with high cholesterol on stable doses of statins who received 300 mg/week of ISIS 301012 for five weeks achieved reductions of 51% in LDL and 41% in triglycerides beyond the levels achieved with statins alone. ISIS 301012 has been well tolerated, both as a single agent and when coadministered with statins.

We are continuing the development of ISIS 301012 in the studies described above at doses up to 400 mg/week. We plan to announce results of these studies in 2007, and also initiate a longer term Phase 2 study for the general high cholesterol patient populations, and a pivotal study to support registration for FH. We intend to license ISIS 301012 to a partner for Phase 3 development, registration and marketing for the general high cholesterol population.

Phase 1 data from clinical studies that we reported in 2006 provide additional support for ISIS 301012's potentially attractive profile as a drug. In March 2006, we reported data from a drug-drug interaction study in which ISIS 301012 did not interact with simvastatin or ezetimibe, currently available lipid lowering drugs with which ISIS 301012 may be dosed in combination. These results suggest that ISIS 301012 is unlikely to interact with other commonly prescribed lipid-lowering drugs, and therefore supports our plan for development as an add-on therapy. In February 2006, we announced that we completed a Phase 1 study of an oral formulation of ISIS 301012 demonstrating oral bioavailability and pharmacological activity of the drug. One month dosing in healthy volunteers with an oral capsule formulation of ISIS 301012 resulted in an average of 6% bioavailability and a statistically significant average reduction of approximately 13% in apoB, and commensurate reductions in LDL as compared to placebo. We are not actively developing the oral formulation at this time, but this study demonstrates the feasibility of oral delivery later in the life cycle of the drug.

In April 2006, we entered into a collaboration with Symphony Capital Partners, L.P. and a group of co-investors to form Symphony GenIsis, Inc., which was capitalized with $75 million to be used exclusively for the development of ISIS 301012 and two diabetes drugs, ISIS 325568, targeting GCGR, and ISIS 377131, targeting GCCR.

- **Our goals for 2007 for ISIS 301012 are to:**
  - **Report results of ISIS 301012 three month monotherapy Phase 2 study (1st quarter)**
  - **Report results of ISIS 301012 five week statin add-on Phase 2 study (1st quarter)**
  - **Report results of ISIS 301012 three month statin add-on Phase 2 study (2nd half)**
  - **Initiate longer-duration Phase 2 study in polygenic high cholesterol patients (2nd half)**
  - **Report results of ISIS 301012 FH Phase 2 Studies (2nd half)**
  - **Initiate registration study for FH (2nd half)**

ISIS 353512—ISIS 353512 is a generation 2.2 antisense inhibitor that targets C-reactive protein, or CRP. Excessive amounts of CRP have been linked to coronary artery disease and a growing body of evidence from clinical trials implicates CRP in cardiovascular disease progression. These results suggest that it may be therapeutically beneficial to significantly decrease CRP levels in patients who are at risk for coronary events.

In preclinical studies, ISIS 353512 produced dramatic suppression of liver and serum CRP levels in monkeys. In additional animal studies, ISIS 353512 dramatically reduced human CRP levels in transgenic mice. Based on these results, we initiated development activities for ISIS 353512.

- **In 2007, our goal for ISIS 353512 is to initiate IND-enabling studies.**

Metabolic Disease

We are pursuing the discovery and development of antisense drugs for metabolic diseases such as diabetes and obesity. These chronic diseases affect millions of people and there continues to be a significant need for new therapies for these patients. We believe that our second generation antisense drugs will have properties that will make them attractive therapies for metabolic diseases. According to the Centers for Disease Control and Prevention (CDC), diabetes affects more than 20 million people in the U.S., or 7% of the population, with type 2 diabetes constituting 90%-95% of those cases.

ISIS 113715—ISIS 113715 is our second generation antisense inhibitor of protein tyrosine phosphatase 1b, or PTP-1b, for the treatment of type 2 diabetes. PTP-1b is responsible for turning off the activated insulin receptor, so by reducing levels of PTP-1b, ISIS 113715 enhances the activity of insulin. Because ISIS 113715 is an insulin sensitizer that acts by increasing the activity of the insulin receptor in response to insulin, the most logical place for this drug in the diabetes treatment regimen is as an adjunct to insulin therapy, and that's how we initially plan to develop this drug for registration. ISIS 113715 presents us with a unique opportunity of being first in class with a novel mechanism of action, as an insulin signal enhancer with anti-obesity and lipid lowering potential.

PTP-1b has long been recognized as an attractive target for treatment of diabetes, but due to structural similarities among closely related proteins, it has been difficult to identify small molecule drugs with sufficient specificity to be safe. Antisense technology allows us to design very specific drugs that inhibit PTP-1b and that do not inhibit other family members, making it possible to reduce PTP-1b activity without having other effects on closely related proteins that would likely lead to unwanted side effects.

In June 2006, we announced positive Phase 2 results in patients with type 2 diabetes treated with ISIS 113715 as a single agent. The study was conducted in newly diagnosed type 2 diabetic patients with moderate diabetes and divided into two parts, a six week safety portion with ascending doses, and a three month portion at a weekly ISIS 113715 dose of 200 mg/week designed to determine the effects of treatment with ISIS 113715 on several measures of blood glucose control. We analyzed the activity of ISIS 113715 in the three month 200 mg/week portion, and showed statistically significant improvements in multiple measures of glucose control along with statistically significant reductions in LDL cholesterol. In this study we did not see a statistically significant improvement in glycosylated hemoglobin, or HbA1c, a measure of long-term glucose control. We believe this reflects the combined factors of small size, short duration and high placebo response rate in the trial, since these were newly-diagnosed diabetics being counseled on diet and exercise modifications for the first time. In the study, ISIS 113715 was well tolerated and did not cause low blood sugar, called hypoglycemia, or weight gain.

We are currently conducting a combination study of ISIS 113715 in patients with type 2 diabetes. Because our initial registration plan for ISIS 113715 is as an adjunct to insulin therapy, we are evaluating it in combination with sulfonylureas. Sulfonylureas, which are commonly prescribed oral antidiabetic drugs, increase insulin secretion in the body and therefore they offer the best approximation of a combination with insulin therapy in the milder disease setting appropriate for this first combination experience with ISIS 113715.

In addition, we are conducting a Phase 2 study of ISIS 113715 in patients with type 2 diabetes to further assess the effects of ISIS 113715 on insulin sensitivity, fasting and post meal time glucose control and lipid metabolism.

- **Our goal for 2007 is to advance our Phase 2 study of ISIS 113715 as an add-on to sulfonylureas.**

ISIS 325568—ISIS 325568 is a generation 2.2 antisense drug that targets GCGR. Glucagon is a hormone that opposes the action of insulin and stimulates the liver to produce glucose. In type 2 diabetes, unopposed action of glucagon can lead to increased blood glucose levels. Reducing the expression of GCGR using antisense inhibitors, and thereby reducing excessive liver glucose production, should lower blood glucose and help control type 2 diabetes.

In preclinical studies, ISIS 325568 produced excellent glucose control and reduced levels of blood triglycerides without producing hypoglycemia. While this is justification enough to pursue GCGR as a therapeutic target, the additional activity of ISIS 325568 in increasing circulating glucagon-like peptide, or GLP-1, makes it an even more attractive drug for development. GLP-1 is a hormone that helps to preserve pancreatic function, enhancing insulin secretion, and like drugs that mimic GLP-1, ISIS 325568 could therefore have disease modifying effects.

The development of ISIS 325568 is funded through clinical proof-of-concept by Symphony GenIsis.

- **In 2007, our goal for ISIS 325568 is to initiate Phase 1 studies (2nd half).**

ISIS 377131—ISIS 377131 is a generation 2.2 antisense drug that targets GCCR. Excessive glucocorticoid action causes a spectrum of clinical features, including obesity, insulin resistance and glucose intolerance. Glucocorticoids promote breakdown of protein and fat from storage and ultimately result in increased liver glucose production. Because of the tissue distribution properties of antisense drugs, with ISIS 377131 we expect to inhibit glucocorticoid signaling selectively in liver and fat tissue, and not in the central nervous system or adrenal glands. We anticipate that ISIS 377131 will improve blood glucose levels and also have lipid-lowering effects. Therefore, this drug may prove to have an attractive profile in treating diabetic dislipidemia and even obesity which often goes hand-in-hand with type 2 diabetes.

In preclinical studies, ISIS 377131 produced pronounced glucose lowering effects, and a robust lowering of blood cholesterol and triglycerides. Furthermore, we also observed a reduction in body fat and reduction of fat build up in the liver. Fatty liver is observed in over 40% of the diabetic population and is believed to contribute to defective insulin action in these patients. We saw no effects of ISIS 377131 on glucocorticoid activity in the brain or other tissues such as the adrenal glands and lymphocytes. Therefore, we expect that the drug will provide significant therapeutic benefit without causing systemic anti-glucocorticoid side effects.

The development of ISIS 377131 is funded through clinical proof-of-concept by Symphony GenIsis.

- **In 2007, our goal for ISIS 377131 is to initiate IND-enabling studies.**

Other Diseases

ISIS 369645—ISIS 369645 is our first drug for the treatment of asthma and related pulmonary diseases, and our first inhaled drug. ISIS 369645 is a second generation antisense inhibitor of the alpha subunit of the interleukin 4 receptor, IL-4R-alpha. Inhibiting the production of IL-4R-alpha inhibits the activity of two important cytokines in asthma, IL-4 and IL-13, which regulate inflammation, mucus overproduction and airway hyper-responsiveness.

In preclinical studies, we have shown that a mouse-optimized antisense inhibitor of IL-4R-alpha potently reduced target mRNA and protein levels, and had pharmacologic activity in mouse models of

asthma that included reducing lung cytokine production, inflammation, and airway hyper-responsiveness. In addition, these studies showed that, when delivered by inhalation, ISIS 369645 rapidly distributed to the airways and achieved therapeutic drug concentrations in multiple cell types with little systemic exposure. Based on these results, we initiated development activities for ISIS 369645.

- **Our goal for 2007 for ISIS 369645 is to initiate IND-enabling studies.**

Our Partners' Drugs in Development

During 2007, we plan to support our partners as they progress their Isis drugs through development.

Cancer

OGX-011—OGX-011 is a second generation antisense inhibitor of clusterin, which we are co-developing and commercializing with OncoGenex. We and OncoGenex designed OGX-011 to inhibit the secreted protein clusterin, which acts as a cell-survival protein and is over-expressed in response to anti-cancer agents, like chemotherapy, hormone ablation and radiation therapy. Based on analysis of human tumor tissue, clusterin is over-expressed in several cancers, including prostate, breast, renal, bladder, non-small cell lung and ovarian. Increased clusterin production is linked to faster rates of cancer progression, treatment resistance and shorter survival duration. In June 2004, OncoGenex announced results of a study evaluating OGX-011 in combination with hormone ablation therapy in patients with high-risk prostate cancer. The Phase 1 study showed that once weekly intravenous administration of OGX-011 was well tolerated, achieved excellent drug concentration in target tissue, and produced a 91% dose-dependent reduction of its target, clusterin, in prostate cancer. OGX-011 is currently in five Phase 2 clinical trials and is being evaluated in combination with chemotherapy in patients with prostate, breast and non-small cell lung cancer. OncoGenex expects that primary endpoint data from all five Phase 2 clinical trials will be available by the end of 2007. It plans to evaluate the results of the Phase 2 studies to determine which cancer indications and which treatment combinations demonstrate promise and will design Phase 3 clinical trials accordingly.

LY2181308—We licensed our anti-cancer drug, LY2181308, to Lilly in 2002, as part of the companies' antisense drug discovery research collaboration in cancer initiated in 2002. This drug targets survivin, which plays a role in cancer cell death, or apoptosis. Survivin is one of the most commonly over expressed proteins in cancers. Our researchers and collaborators have shown that inhibiting the expression of survivin by LY2181308 inhibits the growth of cancer cells. Since normal cells in the body do not express survivin, we expect that this drug will have fewer side effects than traditional chemotherapy. Lilly recently completed its Phase 1 studies of LY2181308, and during 2007, expects to initiate a broad Phase 2 program evaluating LY218308 in several cancers. To date, we have earned $4.1 million in license fees and milestone payments related to the continued development of LY2181308, including the $1.5 million milestone payment we earned when Lilly initiated Phase 1 clinical trials of LY2181308.

LY2275796—LY2275796 is the second antisense anti-cancer drug we have licensed to Lilly and is currently in Phase 1 studies. This drug targets eukaryotic initiation factor-4E, or eIF-4E, a protein involved in tumor progression, angiogenesis and metastases, including breast, head and neck, prostate, lung, bladder, colon, thyroid and non-Hodgkin's lymphomas. Based on scientific literature, there is experimental data supporting that eIF-4E may act as a critical "switch" in cancer progression. In January 2006, Lilly initiated Phase 1 clinical trials of LY2275796 for which we earned a $750,000 milestone payment.

OGX-427—OGX-427, the second anti-cancer drug in our collaboration with OncoGenex, is a second generation antisense inhibitor targeting heat shock protein 27, or Hsp27. Hsp27 is a cell survival protein that is over-produced in response to many cancer treatments, including hormone ablation therapy, chemotherapy and radiation therapy. Increased Hsp27 production is observed in many human cancers, including prostate, non-small cell lung, breast, ovarian, bladder, renal, pancreatic, multiple myeloma and

liver cancers. Increased Hsp27 production is linked to faster rates of cancer progression, treatment resistance and shorter survival duration. In single agent preclinical studies, OGX-427 demonstrated significant anti-tumor activity at low concentrations. In addition, when combined with chemotherapy, in preclinical prostate cancer studies, OGX-427 was able to significantly enhance the anti-tumor activity of the widely used chemotherapy drug, paclitaxel. OncoGenex is currently conducting IND-enabling toxicology and pharmacokinetic studies for OGX-427. During 2007, OncoGenex intends to file its IND and initiate a Phase 1 clinical trial for OGX-427.

Inflammatory Diseases

Alicaforsen (ISIS 2302)—Now under license to Atlantic Healthcare, alicaforsen selectively inhibits ICAM-1 gene expression. Over-expression of ICAM-1 occurs in a wide variety of inflammatory disorders, including ulcerative colitis, or UC, and pouchitis. UC is an inflammatory bowel disease of the colon, a part of the large intestine, and pouchitis is an inflammation of the surgically constructed internal pouch created in UC patients when their diseased colons are removed. In December 2004, we released the results of three Phase 2 studies of alicaforsen enema to treat patients with UC in which alicaforsen was well tolerated and produced significant and long-lasting disease improvement, as measured by changes in Disease Activity Index scores and other indicators of disease. In addition, data from a 2003 clinical trial for an enema formulation of alicaforsen demonstrated an improvement in clinical disease symptoms of up to nine months in patients with pouchitis. In 2007, we licensed alicaforsen to Atlantic Healthcare, initially for pouchitis and eventually for ulcerative colitis and other inflammatory diseases.

ATL1102—ATL1102 is a generation 2.2 antisense inhibitor of CD49d, which is a subunit of Very Late Antigen-4, or VLA-4. Studies in animal models have demonstrated that inhibition of VLA-4 has a positive effect on a number of inflammatory diseases, including multiple sclerosis. In December 2001, we licensed ATL1102 to ATL. Based on the results of a dose-escalating Phase 1 study of ATL1102 that showed that 6 mg/kg/week of ATL1102 appeared well tolerated, ATL initiated a Phase 2 clinical trial of ATL1102 in patients with multiple sclerosis, which is currently ongoing.

Other Diseases

Vitravene, or fomivirsen—In August 1998, the FDA approved Vitravene, an antisense drug that we discovered and developed, to treat CMV retinitis in AIDS patients. Novartis Ophthalmics AG, our worldwide distribution partner for this drug, launched Vitravene in November 1998. New anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, have prolonged survival in HIV-infected individuals. This has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections, including CMV retinitis. As a result, Novartis no longer markets Vitravene. Vitravene demonstrates our ability to meet FDA and European regulatory requirements for safety and efficacy, and for the commercial manufacture of antisense drugs.

Merck Drug—This drug, which inhibits hepatitis C virus replication, resulted from a drug discovery collaboration between Merck and us. Merck initiated Phase 1 development in November 2006, for which we earned a $1 million milestone payment.

iCo 007—We licensed iCo 007 to iCo for the treatment of various eye diseases that occur as complications of diabetes including diabetic macular edema and diabetic retinopathy. iCo 007 is an antisense inhibitor of c-Raf kinase. In preclinical studies, antisense inhibition of c-Raf kinase was associated with a reduction in the formation and leakage of new blood vessels in the eye, suggesting c-Raf kinase inhibition could be valuable in the treatment of both diabetic macular edema and diabetic retinopathy. Diabetic retinopathy is one of the leading causes of blindness in people in the U.S., and by age 20 nearly 100% of type 1 diabetics and between 50% and 80% of type 2 diabetics have evidence of

retinopathy. In 2006, iCo filed an IND for iCo 007, for which we earned a milestone payment, and in 2007 iCo plans to initiate a Phase 1 clinical study of iCo 007 in diabetic macular edema.

ISIS 333611—ISIS 333611 is our first drug to enter development for the treatment of neurodegenerative diseases. The drug is being developed in a formulation that is administered directly into the central nervous system by a small pump that infuses drug into the cerebral spinal fluid. This type of administration is called intrathecal infusion. In animal models, researchers have demonstrated that our second generation drug, ISIS 333611, when delivered into the cerebral spinal fluid, inhibits Cu/Zn superoxide dismutase, or SOD1, a molecule that is associated with an inherited, aggressive form of amyotrophic lateral sclerosis, or ALS, which is also known as Lou Gehrig's disease. In July 2006, researchers reported in the Journal of Clinical Investigation that treatment with ISIS 333611 prolongs life in rats that show many features of ALS. By delivering ISIS 333611 directly to the cerebral spinal fluid that circulates inside the brain, investigators were able to lower production of the mutant protein in neurons and surrounding cells. Similar results were obtained in both small and large laboratory animals. The ALS Association is funding a safety study of ISIS 333611 in preclinical monkeys.

ISIS 5320—ISIS 5320, a phosphorothioate oligonucleotide aptamer drug, specifically and potently inhibits the attachment of HIV to target cells by physically interfering with the interaction of the HIV receptor gp120 with CD4 on target cells. In 2006, we licensed ISIS 5320 to ImQuest Pharmaceuticals, Inc. The safety of ISIS 5320 has been demonstrated in human clinical trials as a treatment for systemic HIV infection and thus ImQuest projects that the time to develop the agent as a topical microbicide will be significantly shortened, allowing the microbicide to enter human clinical trials in 2007.

ATL1103—ATL1103 is a second generation antisense drug targeting growth hormone receptor, or GHr. Consequently, it reduces the levels of circulating insulin-like growth factor-1, or IGF-1, produced in the liver, which is a hormone that contributes to various diseases including the growth disorder acromegaly, which is characterized by abnormal growth of organs, face, hands and feet, as well as for diabetic retinopathy, a common disease of the eye and a leading cause of blindness. In animal studies, ATL1103 demonstrated significant reductions in IGF-1 levels in the blood. ATL is planning to initiate IND-enabling studies of ATL1103 in 2007.

Technology Research Programs

Using proprietary antisense oligonucleotides to identify what a gene does, called gene functionalization, and then determining whether a specific gene is a good target for drug discovery, called target validation, are the first steps in our drug discovery process. We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. Furthermore, because of the nature of antisense drugs, the very molecules we design for gene functionalization and target validation experiments may become our lead drug candidates. This efficiency is a unique advantage of our antisense drug discovery. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology. Through the efforts of our scientists in the antisense drug discovery group, we have produced second generation antisense drugs that have increased potency and stability. We combine our core technology programs in medicinal chemistry, RNA biochemistry, and molecular and cellular biology with molecular target-focused drug discovery efforts to design drugs. The goal of our target-based research programs is to identify antisense drugs to treat diseases for which there are substantial markets and for which there is a need for better drugs. In addition, our research programs focus on identifying next-generation compounds to serve as backup compounds to our current drugs in development and to our development candidates.

Our core technology programs can support multiple target-based antisense research programs without significantly increasing costs. Through these programs, we can efficiently explore numerous disease targets and identify lead compounds to advance into preclinical development. We are currently pursuing antisense

drug discovery programs focused on various cardiovascular, metabolic and inflammatory disease targets, and cancer.

Additionally, we are pursuing early-stage antisense mechanisms, including RNA interference, or RNAi, microRNA, and alternative splicing, through satellite company research collaborations and partnerships like those we have with Alnylam, Rosetta Genomics and Ercole.

RNAi is an antisense mechanism that involves using a small interfering RNA, or siRNA, as a method to target a mRNA sequence. With siRNA, the cell utilizes a protein complex called RISC to prevent the production of a disease-causing protein. We have a strong and growing intellectual property position in RNAi methodology and oligonucleotide chemistry for siRNA therapeutics, and we have licensed these patents to Alnylam for double-stranded siRNA therapeutics, as part of our collaboration with them. We are also developing technology for creating single-stranded siRNA drugs, which falls outside the scope of our license to Alnylam. At present the double-stranded siRNA drugs in development are administered locally, or, to achieve sufficient systemic delivery, require special chemical formulation of the oligonucleotides. In contrast, our single-stranded second generation antisense drugs readily distribute to target organs including liver and kidney, and we are evaluating the feasibility of developing similarly well-behaved single-stranded RNA-like oligonucleotide drugs that act through the siRNA mechanism.

MicroRNAs are an emerging class of drug targets and a new area for drug discovery. MicroRNAs are small RNA molecules that work as natural antisense oligonucleotides and appear to have critical functions in controlling the process of gene expression. These molecules may serve as drug targets or as drugs themselves. Researchers estimate that there are more than 600 microRNA molecules in humans. In 2006, we presented results of preclinical studies demonstrating that inhibition of miR-122, a liver-specific microRNA, by a second generation antisense drug significantly improved high cholesterol, fatty liver, and liver function without affecting blood sugar levels in diabetic mouse models, demonstrating that antisense inhibition is a powerful technique to regulate the function of microRNAs and suggesting that miR-122 may be an attractive therapeutic target. We have 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.

Modulation of alternative splicing seeks to control the process by which a single gene can lead to several proteins. To be converted into proteins, genes must be initially copied into a pre-mRNA. Pre-mRNA often contains extra sequence information that must be removed prior to translation into the protein. This process is called splicing. Using antisense technology, we have been able to control how these stretches of RNA are spliced back together. This provides another way to control the production of a disease-causing protein. Through our multi-year collaboration with Ercole, we are combining both companies' alternative splicing expertise to discover antisense drugs that regulate RNA splicing.

Ibis Biosciences, Inc.

Over the last seven years, within our Ibis business, we have developed a biosensor system, called the Ibis T5000 Biosensor System, that has the potential to revolutionize the identification of infectious diseases. The Ibis T5000 Biosensor System emerged from technology that Ibis was originally pursuing for RNA targeted drug discovery. Supported by substantial government funding, Ibis applied this technology to develop a system that can simultaneously identify a broad range of infectious organisms in a single sample without needing to know beforehand what might be present in the sample. Organisms might be previously unknown, may have been genetically altered, or may be impossible to grow in the laboratory for identification through culturing. Through our Ibis subsidiary, we plan to commercialize the Ibis T5000 Biosensor System and related assay kits. The commercial applications for the Ibis T5000 Biosensor System include biodefense, forensics, epidemiological surveillance, infectious disease research, hospital-acquired infection control and *in vitro* diagnostics. Ibis achieved an important milestone in implementing its

commercialization plan when, in December 2006, Ibis placed its first commercial system. In addition, Ibis has delivered four prototype systems to its government partners for use in biodefense, forensics and epidemiological surveillance.

How the Ibis T5000 Biosensor System Works

The Ibis T5000 Biosensor System works by using our proprietary primers to amplify unique DNA sequences in samples, weighing the amplified products with mass spectrometry, and comparing the resulting weights against a database of organisms. This process allows the Ibis T5000 Biosensor System to rapidly identify a broad range of the many thousands of species of infectious organisms, as well as previously unknown agents that are in a sample. Once the analysis is complete, our system provides a simple, easy to read report that includes the organisms that are in the sample and the quantities of each organism present. In addition, the Ibis T5000 Biosensor System can tell an investigator or physician if there is a previously unidentified organism in the sample and how it is related to organisms previously encountered. We have demonstrated the Ibis T5000 Biosensor System can identify a variety of bacteria and viruses in both environmental and human clinical samples.

The Ibis T5000 Biosensor System's ability to rapidly identify newly emerging organisms, down to the strain level, can provide public health officials and physicians with the critical information necessary to help track the spread of an infection, and ultimately, to contain it. The Ibis T5000 Biosensor System can also identify viruses, including mutated forms and previously unknown forms, which may not be identifiable with traditional test methods. In addition, the system can identify co-pathogens associated with an infection, which frequently contribute to rapidly spreading and severe infections. This information may allow physicians to effectively treat an infection with the potential not only to decrease mortality and severity of infections, but also to contain their spread.

Ibis' Commercialization Strategy

Ibis' commercialization plan is a phased commercial development process that takes advantage of near-term opportunities, builds on an existing customer base and moves toward the larger healthcare markets. Through our Ibis subsidiary, we plan to initially commercialize the Ibis T5000 Biosensor System and related products for use in markets such as biodefense, forensics, epidemiological surveillance, infectious disease research, and most importantly, hospital-associated infection control. These near-term, non-regulated market opportunities may provide a path into the regulated *in vitro* diagnostics market. We intend to enter the *in vitro* diagnostics market through a strategic alliance with an industry-leading IVD partner.

The first phase of this commercialization plan involves selling Ibis T5000 Biosensor Systems and assay kits to government customers for biodefense, forensics and epidemiological surveillance. In December 2006, we took an important step in our commercialization plan for Ibis by delivering our first Ibis T5000 Biosensor System to a U.S. government agency for human forensics applications. We expect to deliver the second system under this order by early 2007. Additionally, during 2005 and 2006, we placed four prototype biosensor systems with our government partners, each for a different application. We delivered our first biosensor system to the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) for use in biodefense. We have also delivered a system to the Department of Homeland Security's (DHS) National Bioforensic Analysis Center for use in microbial forensics, a system to the Naval Health Research Center for use in respiratory disease surveillance and a system to the Centers for Disease Control and Prevention (CDC) for epidemiological surveillance. Because these government agencies provided funding for the development of the Ibis T5000 Biosensor System, we provide the initial products as part of our ongoing government contracts. However, after the contract amounts are met, we expect our government customers to continue to purchase assay kits to use with their Ibis biosensor systems.

We are advancing our commercialization plan to develop and commercialize Ibis T5000 Biosensor Systems and related products for the hospital-associated infection control markets by continuing to work with government and non-government collaborators to develop applications to identify and track infectious organisms that cause hospital-associated infections. Hospital-associated infections, also known as nosocomial infections, are contracted after entering the hospital and include sepsis, urinary tract infections, pneumonia, and infections after surgery.

Building on the successes of our early commercialization efforts, we plan to develop applications for *in vitro* diagnostics. When we enter the *in vitro* diagnostic market, we expect to enter it with a leading industry partner and in stages. First, we plan to develop assay kits for difficult to diagnose and potentially lethal infectious diseases for which there are no relevant current detection technologies that operate on a time-scale to allow life saving responses. As we gain experience and acceptance with these products, we will then move to diseases where there are existing diagnostic methods, which we will need to displace.

We plan to focus on the high-volume, high-margin consumables opportunity through the sale of assay kits and related products to our customers. Although we are assembling instruments for our initial customers, we are transitioning the manufacturing, sales and support responsibilities for the Ibis T5000 instruments to our instrument manufacturer, Bruker Daltonics Inc., a subsidiary of Bruker Biosciences Corporation. In this way, we are limiting our investment in instrument design and service. In addition, we believe that by partnering with Bruker Daltonics we will be able to enter the market more rapidly than we could on our own. We also believe we will need a more limited investment to create the infrastructure to make and sell assay kits than we would need to manufacture and support Ibis T5000 instruments.

Ibis achieved a second important milestone in implementing its commercialization plan when, in the third quarter of 2006, Ibis received a contract worth up to $1.9 million to analyze samples in its assay services laboratory. Ibis' assay services laboratory represents a key part of the early Ibis business strategy by providing revenue to support initial commercialization activities while instrument installations and kit sales increase. In addition, we expect that the assay services laboratory will support the Ibis T5000 sales process by providing customers the opportunity to evaluate the capabilities of the Ibis T5000 Biosensor System prior to making a buying decision.

Continued Development Activities

Our Ibis subsidiary will continue to develop the Ibis T5000 Biosensor System and applications through its contracts with government agencies, including the Defense Advanced Research Projects Agency (DARPA), the DHS, the CDC, the Federal Bureau of Investigation (FBI) and the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH). Each of these agencies represents a significant source of funding for Ibis. As of December 31, 2006, we had earned $57.5 million in revenue under our government contracts and grants, and we had an additional $7.3 million committed under our existing contracts and grants. We may receive continued funding under these contracts based upon a variety of factors, including the accomplishment of program objectives and the exercise of additional contract options by the contracting agencies. However, 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.

During 2006 and 2005, revenue generated from agencies of the United States Government totaled 37% and 30%, respectively, of our total revenue. Please refer to Note 7, "Segment Information and Concentration of Business Risk," starting on page F-39 of this report on Form 10-K for additional information about our Ibis subsidiary.

- **Our 2007 goals for our Ibis subsidiary are to:**
  - **Transfer instrument manufacturing to Bruker Daltonics**
  - **Place at least eight new instruments**

Collaborative Arrangements and Licensing Agreements

Partnership Strategy

Overview

Over the past 18 years we have built a business with expertise in RNA-based research, drug discovery and development. Our strategy is to outlicense our drugs at value inflection points and build a growing annuity of milestone and royalty income, and take advantage of others' existing infrastructure for marketing and selling drugs. With the pioneering work we have done in developing our technology platform, we can discover and validate many more drug candidates than we can advance ourselves. For key therapeutic areas, including cardiovascular and metabolic diseases, we internally develop our drugs to a point where we believe we have established significant value. We license our drugs that fall outside our strategic therapeutic areas of focus to partners at an earlier stage of development. This practice has led to our expansive external pipeline with multiple partnership franchises in cancer, inflammation and other disease areas. In the cancer area alone, both Lilly and OncoGenex each have two of our drugs in development. This strategy has allowed us to build a clinical development pipeline of 17 drugs, which we believe is a significant achievement for a company our size.

We have a broad patent portfolio covering our products and technologies. We own or exclusively license more than 1,500 issued patents, which we believe represents the largest and most valuable antisense and RNA-oriented patent estate in the pharmaceutical industry. The principal purpose of our intellectual property portfolio is to protect our products and those of our partners. In addition, our intellectual property is a strategic asset that we are exploiting to generate near-term revenues and that we expect will also provide us with revenue in the future. Our intellectual property portfolio enables us to expand our pipeline by granting to other companies limited access to antisense technology through licenses. Partnerships include traditionally structured drug development and commercialization licenses, discovery and development collaborations, research and technology collaborations, and intellectual property licenses. Some of these partnerships are with large pharmaceutical companies like Lilly, Merck and Pfizer, while others are satellite company partnerships, which we discuss below.

Satellite Company Strategy

Our expertise and intellectual property position in RNA-based therapeutics has repeatedly produced more opportunities than we can afford to develop on our own. Internally we are focused on developing drugs for cardiovascular and metabolic disease indications to later stage value inflection points, and we place earlier stage drugs for cancer, inflammatory, and other disease indications in the hands of partners who can enhance the opportunities with their own expertise and focused research and development efforts. In return, we share our expertise and intellectual property position in RNA-based therapeutics and take an ownership interest in the resulting products and/or the partner company. Through these relationships, we can continue to expand the reach and potential of RNA-based therapeutics and share in the potential success of multiple companies and products.

Because these companies work closely together with us, with the common goals of advancing the technology and/or pipeline, we refer to these companies as our satellite companies, and this strategy as our satellite company strategy. Our satellite company strategy allows us to create a much broader product pipeline than we could develop on our own.

These satellite companies generally fall into two categories. The first category includes companies that in-license a drug discovered by us, and agree to continue developing the product. Examples of these types of product-based satellite company drug discovery and development partners are ATL, iCo, OncoGenex, and ImQuest. The second category includes companies that are focused on advancing emerging antisense technologies. These collaborations typically involve a cross-license between us and our partner so that each party has access to technology that is useful or necessary to advance the particular approach. This strategy allows us to participate in newly emerging approaches to RNA-based therapeutics and augment our active programs in these areas. Examples of our satellite company technology research collaborators are Alnylam, working on RNA interference, Ercole, working on alternative splicing, and Rosetta Genomics, working on microRNA.

Technology and Intellectual Property Licensing

Further, we have an active intellectual property licensing program in which we license aspects of our intellectual property to companies like Idera Pharmaceuticals, Inc. (formerly Hybridon, Inc.), Integrated DNA Technologies, Inc., Roche Molecular Systems, Atugen AG, and Dharmacon, Inc. Through this program, we also license our non-antisense patents as we did with Eyetech Pharmaceuticals, Inc., a wholly owned subsidiary of OSI Pharmaceuticals, Inc. As of December 31, 2006, we had generated more than $77 million from our intellectual property licensing program that helps support our internal drug discovery and development programs.

Antisense Drug Discovery Collaborations

Symphony GenIsis, Inc.

On April 7, 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 drugs from our metabolic disease program, ISIS 325568, targeting GCGR, and ISIS 377131, targeting GCCR. 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 the development of ISIS 325568 and ISIS 377131 through initial proof-of-concept in human clinical trials. In addition to providing the financial support to move these three drugs forward, the transaction allows us to continue to control and manage the development of these 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, GCGR and GCCR programs. We have received an exclusive purchase option from Symphony GenIsis' investors that allows 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. We may pay the purchase option exercise price 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 60-day average trading price prior to the grant, which was $7.14. To compensate

Symphony Capital for structuring the transaction and to pay a portion of its expenses, we paid structuring and legal fees of $4.1 million.

The Ludwig Institute; Center for Neurological Studies

In October 2005, we entered a collaboration agreement with the Ludwig Institute, the CNS and researchers from these institutions to discover and develop antisense drugs in the areas of ALS and other neurodegenerative diseases. Under this agreement, we agreed to pay the Ludwig Institute and CNS royalties and modest milestones on any antisense drugs discovered and developed within the collaboration. The researchers from the Ludwig Institute and CNS, through funding from the ALS Association, will conduct preclinical safety and efficacy studies of ISIS 333611.

Pfizer, Inc

In May 2005, we entered into a multi-year drug discovery collaboration with Pfizer to identify second generation antisense drugs for the treatment of ophthalmic disease. Under the terms of the agreement, we received a technology access fee of $1.0 million. To date, we have earned milestone payments totaling $1.2 million under the collaboration. Pfizer will also pay us additional milestone payments if key research, clinical, regulatory and sales milestones are achieved, and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug for the first indication, we will earn milestone payments totaling up to $26.1 million. In addition, we will receive royalties on the sale of drugs resulting from the collaboration.

Eli Lilly and Company

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

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

As part of the collaboration, Lilly licensed LY2181308, our antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eIF-4E. To date, we have earned $4.1 million and $1.5 million in license fees and milestone payments related to the continued development of LY2181308 and LY2275796, respectively. We will receive additional milestone payments aggregating up to $25.0 million and $19.5 million if LY2181308 and LY2275796, respectively, achieve specified regulatory and commercial milestones. In addition, we will receive royalties on future product sales of these drugs.

As part of the collaboration extension, we are exploring with Lilly antisense drugs targeting Signal Transducer and Activator of Transcription 3, or STAT-3, a protein that regulates cell division and growth, and prevents cell death. We are working closely with Lilly to advance a STAT-3 candidate into development.

Our relationship with Lilly historically provided several revenue sources, including research funding related to the $100 million research loan and development milestones similar to the milestones for

LY2181308 and LY2275796. During 2006, 2005, and 2004, we generated revenue from our relationship with Lilly totaling $1.2 million, $10.8 million, and $15.7 million, respectively, which comprised 5%, 27%, and 37%, respectively, of our total revenue during those same periods.

Merck & Co., Inc.

In June 1998, we entered into a multi-year research collaboration and license agreement with Merck to discover small molecule drug candidates to treat patients infected with HCV. The research collaboration ended in May 2003 in accordance with its terms. However, in December 2006, Merck advanced a drug discovered in this collaboration into Phase 1 clinical trials for which we earned a $1 million milestone payment. In addition, Merck will pay us aggregate milestone payments of up to $16 million upon the achievement of key clinical and regulatory milestones, and royalties on future product sales.

Satellite Company Drug Discovery and Development Collaborations

Achaogen, Inc.

In January 2006, we licensed our 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. In exchange for the exclusive, worldwide license to our aminoglycoside program, Achaogen issued to us $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, we will receive milestone payments totaling up to $34.5 million for the achievement of key clinical, regulatory and sales milestones. In addition, we 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.

Antisense Therapeutics Limited

In December 2001, we licensed ATL1102 to ATL; an Australian company publicly traded on the Australian Stock Exchange. We were responsible for completing the required preclinical studies for ATL1102 and for manufacturing the drug for human clinical trials at ATL's expense. ATL agreed to undertake the future clinical development and commercialization of the drug. ATL1102 is currently in Phase 2 clinical trials in patients with relapsing remitting multiple sclerosis.

In addition to ATL1102, ATL is currently developing ATL1103 for growth and site disorders. ATL1103 is a product of our joint antisense drug discovery and development collaboration, which we recently extended for an additional two years. ATL pays us for access to our antisense expertise and for research and manufacturing services we may provide them during the collaboration. Additionally, ATL will pay royalties to us on any antisense drugs discovered and developed within the partnership. We currently own less than 10% of ATL's equity.

Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Healthcare (UK) Limited, a UK-based company that was founded in 2006 by gastrointestinal drug developers to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Healthcare plans to initially develop alicaforsen for pouchitis, an ulcerative colitis indication, followed by ulcerative colitis and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we will receive an upfront payment from Atlantic Healthcare in the form of equity valued at $2 million. In addition, assuming Atlantic Healthcare successfully develops and commercializes alicaforsen, we will receive milestone payments and royalties on future product sales of alicaforsen. If Atlantic Healthcare meets certain of these milestones, at Atlantic

Healthcare's request, we will attempt to identify a second generation lead drug candidate for Atlantic Healthcare. Atlantic Healthcare may take an exclusive worldwide license to the lead candidate under the terms and conditions of the agreement. Atlantic Healthcare is solely responsible for the continued development of alicaforsen, and, if selected, the second generation lead drug candidate.

iCo Therapeutics, Inc.

In August 2005, we granted a license to iCo for the development and commercialization of iCo 007, a second generation antisense drug. iCo is initially developing iCo 007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels such as diabetic macular edema and diabetic retinopathy. iCo paid us a $500,000 upfront fee consisting of $250,000 in cash and a $250,000 convertible note. iCo will pay us milestone payments totaling up to $23 million for the achievement of clinical and regulatory milestones. In addition, we will receive royalties on any product sales of this drug. Under the terms of the agreement, iCo is solely responsible for the clinical development and commercialization of the drug. In December 2006, iCo filed an IND application with the FDA for iCo 007 for which we earned a milestone payment.

In December 2005, we entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo purchased drug manufactured by us for $700,000. iCo made a $525,000 prepayment to us consisting of $175,000 in cash and a $350,000 convertible note. In December 2006, our obligations under the manufacturing and supply agreement were completed and title of the product transferred to iCo. As a result, in January 2007, iCo paid us the remaining balance of $175,000. In May 2006, we received 869,025 shares of iCo common stock for the conversion of both convertible notes.

ImQuest Pharmaceuticals, Inc.

In April 2006, we 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, we will receive royalties on sales of drugs resulting from ISIS 5320. In addition, if ImQuest sublicenses ISIS 5320, we are entitled to a portion of the consideration received.

OncoGenex Technologies Inc.

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

In September 2003, we and OncoGenex expanded our antisense drug development partnership to include the development of the second generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for the preclinical and clinical development of the drug. OncoGenex issued us OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay us milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and pay us royalties on product sales. As of December 31, 2006, OncoGenex had not triggered any of these milestone payments related to OGX-225.

In January 2005, we further broadened our antisense drug development partnership with OncoGenex to allow for the development of two additional second generation antisense anti-cancer drugs. Under the terms of the agreement, OncoGenex is responsible for the preclinical and clinical development of the drugs. In April 2005, OncoGenex selected its first drug under this expansion, OGX-427. OGX-427 targets heat shock protein 27, or Hsp27, which is over-expressed in numerous tumor types and is associated with treatment resistance through its ability to help cancer cells survive stress-induced injury. OncoGenex paid us an upfront fee with a convertible note, which in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will also pay us milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs.

As of December 31, 2006 our ownership interest in OncoGenex was less than 10%.

Sarissa, Inc.

In February 2005, we licensed an anti-cancer antisense drug to Sarissa, a biotechnology company emerging from the University of Western Ontario. The drug is an antisense inhibitor of thymidylate synthase, or TS, a drug target that protects cancer cells from the effects of several chemotherapy treatments. In preclinical studies, antisense inhibition of TS suppressed human tumor cell growth and overcame tumor cell resistance to marketed TS-targeted drugs.

Under the terms of the agreement, Sarissa paid us a $1.0 million upfront fee in exchange for the exclusive, worldwide license to the TS antisense drug. Sarissa paid the upfront fee with a convertible note, which will convert into Sarissa stock upon Sarissa's successful completion of a venture capital financing. Sarissa will also pay us milestone payments totaling up to $5.5 million for the achievement of clinical and regulatory milestones. In addition, we will receive royalties on any sales of the TS antisense drug. Sarissa is solely responsible for preclinical and clinical development of the drug.

Satellite Company Technology Research Collaborations

Alnylam Pharmaceuticals, Inc.

In March 2004, we entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, we exclusively licensed to Alnylam our patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5.0 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug developed by Alnylam under this alliance, the potential milestone payments from Alnylam total $3.4 million and are payable to us upon the occurrence of specified development and regulatory events. We retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. We also made a $10 million equity investment in Alnylam.

In turn, Alnylam nonexclusively licensed to us its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double-stranded RNAi compounds. We also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on either an exclusive or co-exclusive basis depending on the target. If we develop or commercialize an RNAi-based drug using Alnylam's technology, we will pay Alnylam milestones and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million and are payable by us upon the occurrence of specified development and regulatory events. As of December 31, 2006, we did not have an RNAi-based drug in clinical development. As part of the collaboration, each party granted the other party a nonexclusive cross license to its respective patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for microRNA therapeutics.

Our Alnylam alliance provides us with an opportunity to realize substantial value from our pioneering work in antisense mechanisms and oligonucleotide chemistry and is an example of our strategy to participate in all areas of RNA-based drug discovery. To date, we have earned approximately $5.0 million from Alnylam resulting from sublicenses of our technology for the development of RNA interference therapeutics that Alnylam has granted to pharmaceutical partners.

In September 2004, we recorded a non-cash loss on investment of $5.0 million related to the impairment of our equity investment in Alnylam. The loss on investment reflected a decrease in the market value of Alnylam's stock in 2004, which we believe was primarily a result of financial market conditions related to biotechnology companies. Alnylam's stock is currently trading significantly above its 2004 levels, which we believe reflects Alnylam's leading position in the field of RNAi. During 2006 and 2005, we sold a portion of our Alnylam stock resulting in net proceeds of $4.4 million and $2.6 million, respectively. We still hold approximately 290,000 shares of Alnylam's stock.

During 2006, 2005 and 2004, we generated revenue from our relationship with Alnylam totaling $750,000, $3.7 million and $5.5 million, respectively, representing 3%, 9% and 13%, respectively, of our total revenue for those years.

Ercole Biotech, Inc.

In May 2003, we and Ercole initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. Part of this collaboration includes a cross-license of our respective splicing-related intellectual property with Ercole. We are combining our alternative splicing expertise with Ercole's to discover antisense drugs that regulate alternative RNA splicing. As part of this collaboration, we granted Ercole a license to our Bcl-x molecule and certain of our chemistry patents. In addition, we took an equity ownership position in Ercole with the initial funding, in the form of a convertible note, which the companies anticipate will convert into securities that Ercole issues in its next venture capital financing. We also have the option to make an additional equity investment in Ercole. Pursuant to the terms of a Note and Warrant Purchase Agreement, during 2003 and early 2004, we made cash payments to Ercole of $500,000 and $250,000, respectively, in exchange for a convertible note. We expensed the payments when made. The note is secured by all of Ercole's assets, including intellectual property and licenses. The note will convert into securities that Ercole issues in a qualified financing, as defined by the agreement.

Rosetta Genomics, Ltd.

In January 2006, we 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, we and Rosetta will mutually agree on a development strategy for the drug. This collaboration has an initial term of two years.

Santaris Pharma A/S (formerly Pantheco A/S)

In November 1998 and September 2000, we entered into license agreements with Santaris, formerly Pantheco. We amended, restated and consolidated both agreements into a single agreement in May 2003. Under the terms of the amended and restated license agreement, we licensed our novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Santaris on a limited exclusive basis to develop products. The license restricts Santaris to a limited number of molecular targets that are subject to our approval. Santaris has agreed to pay us royalties on any products developed under the license.

As part of our original license agreements with Pantheco, we received shares of Pantheco stock. In May 2003, Pantheco and Cureon A/S merged to form Santaris. Prior to the merger, we purchased additional shares of Pantheco for $55,000 as a result of anti-dilution provisions related to Pantheco's stock. After the merger and as of December 31, 2006, our ownership interest in Santaris was less than 10%.

Intellectual Property Licensing Agreements

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

In May 2001, we entered into an agreement with Hybridon under which we acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to our suite of RNase H patents. In exchange for the license to Hybridon's antisense patents, we paid $15 million in cash and agreed to pay Hybridon $19.5 million in our common stock before May 2003. In return for access to our patents, Hybridon agreed to pay us $6 million in Hybridon common stock before May 2004. During 2004 and 2005, we sold all of our Hybridon stock for net proceeds of approximately $665,000. In September 2005, Hybridon changed its name to Idera Pharmaceuticals, Inc.

Integrated DNA Technologies, Inc.

In March 1999, we further solidified our intellectual property leadership position in antisense technology by licensing certain antisense patents from IDT, a leading supplier of antisense inhibitors for research. The patents we licensed from IDT are useful in functional genomics and in making certain antisense drugs. In December 2001, we expanded this license agreement to allow us to exclusively sublicense this intellectual property for functional genomics purposes. Under the license, we paid IDT $4.9 million in license fees and will pay royalties on drugs utilizing the technology IDT licensed to us.

In addition, in December 2001 we established a long-term research-scale antisense inhibitor supply agreement with IDT. In this supply agreement IDT agreed to manufacture research-scale antisense inhibitors and research reagents to our specifications. We paid IDT $5 million toward our future purchase of antisense inhibitors. During 2004, we recorded a non-cash charge of $4.2 million to write off the unused portion as part of our restructuring activities.

Out-Licensing Arrangements; Royalty Sharing Agreements

Drug Royalty USA, Inc.

In December 2004, we sold a portion of our royalty rights in Macugen to DRC. In exchange for this sale, DRC has paid us $15 million to date and agreed to pay us an additional $9 million in the fourth quarter of 2007. Under the terms of the agreement, we and DRC will share the royalty rights on Macugen through 2009. After 2009, we retain all royalties for Macugen under our Eyetech agreement described below. Under the agreement, through 2009, DRC will receive the royalties on the first $500 million of annual sales of Macugen. We and DRC will each receive 50 percent of royalties on annual sales between $500 million and $1 billion. We retain 90 percent of all royalties on annual sales in excess of $1 billion and 100 percent of all royalties after 2009. We have retained all milestones payable to us by Eyetech under the license agreement.

As part of the sale, we agreed to pay DRC liquidated damages if any one of a defined set of defaults occurs. The amount of liquidated damages will be calculated such that DRC will receive a ten per cent per annum return, compounded quarterly on the total of all purchase price payments made by DRC to us through the default date minus the total of any royalties received by DRC through the default date. To date, DRC has received royalties of $5.8 million. In addition, DRC may withhold any installment of the purchase price if immediately prior to such payment, we fail to meet a minimum liquidity requirement equal to the then outstanding balance on our loan with Silicon Valley Bank; plus the potential amount of liquidated damages, assuming that DRC has paid the impending purchase price installment; plus our cash burn over the most recent three months. As collateral for our obligations under the sale agreement, we

granted DRC a first priority security interest in the patents licensed by us to Eyetech under the license agreement and in the license agreement itself.

Eyetech Pharmaceuticals, Inc.

In December 2001, we licensed to Eyetech, now a wholly owned subsidiary of OSI Pharmaceuticals, Inc., certain of our patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is co-developing and commercializing with Pfizer. Eyetech paid us a $2 million upfront fee and agreed to pay us milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from us.

During 2004, we earned $4 million in milestones associated with the filing of an NDA and FDA approval for Macugen for the treatment of wet age-related macular degeneration. Our license with Eyetech will also generate additional milestone payments aggregating up to $2.8 million for the achievement of specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication.

Roche Molecular Systems

In October 2000, we licensed some of our novel chemistry patents to Roche, a business unit of Roche Diagnostics, for use in the production of Roche's diagnostic products. The royalty-bearing license grants Roche non-exclusive worldwide access to some of our proprietary chemistries in exchange for initial and ongoing payments from Roche to us.

Ibis Collaborations

We developed, within Ibis, the Ibis T5000 Biosensor System with substantial funding from government agencies. We continue to work with government collaborators to further develop the Ibis technology and applications for the Ibis T5000 Biosensor System. We are now commercializing the Ibis T5000 instrument, assay kits, and our assay services to both government and non-government customers.

Commercial Agreements

We plan to work with partners to manufacture, install and support Ibis T5000 instruments. For research markets we are working with Bruker to accomplish this. We expect in the future to work with a partner to complete development, regulatory approval, and then market the Ibis instruments for the *in vitro* diagnostics market. We plan to focus on the manufacture and sale of high-volume, high-margin consumables. We also generate commercial revenue through our assay services laboratory, in which we analyze customers' samples in our own facilities, providing prospective instrument customers the opportunity to assess the Ibis T5000 Biosensor System's capabilities before purchasing an instrument.

Bruker Daltonics Inc.

In July 2006, we entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker Daltonics 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 Daltonics will have exclusive rights to sell Ibis T5000 systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. Ibis has maintained worldwide marketing rights to the diagnostics market.

Assay Services Collaboration

Ibis received a contract to perform forensic analyses of up to 10,000 samples in its assay services laboratory. Revenue from this contract could be up to $1.9 million. This assay services capability represents a key part of the Ibis business strategy, as it not only has the potential to be an important revenue-generating opportunity for the business, but also represents an important resource for customers evaluating the capabilities of the Ibis T5000 and collaborating in applications development.

Research and Development Collaborations

To develop the Ibis T5000 Biosensor System and its applications, Ibis received contracts and grants from a number of government agencies, including DARPA, DHS, CDC, and the NIAID, a part of the NIH. Government collaborations continue to represent a significant source of funding for the Ibis T5000 program. As a result of these collaborations, we are now developing various applications for the Ibis T5000 Biosensor System that we will sell to commercial customers, including government collaborators.

Biodefense

The earliest application of the Ibis T5000 Biosensor System to be funded by the government focused on bioagent detection. In March 2004, Ibis received a two-year contract from DARPA under a subcontract from Science Applications International Corporation, or SAIC, to further develop the Ibis biosensor system to identify infectious agents in biological warfare attacks. As part of this program, Ibis successfully demonstrated proof-of-principle of the Ibis biosensor system by identifying a variety of bacteria and viruses in both environmental and human clinical samples. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis delivered its first Ibis biosensor system to USAMRIID for use in biodefense.

Forensics

In addition to our commercial agreements relating to human forensics, we also have government collaborations related to microbial forensic applications. Microbial forensics is a type of forensics used to investigate crimes involving infectious organisms. Microbial forensics uses the "biological fingerprint" of an infectious organism to help pinpoint the source, allowing law enforcement and public health officials to effectively respond to a biological threat. Additionally, through a government grant, Ibis is continuing its ongoing development of an informational database on microbial agents. The program is a database of biological threat agents, their DNA sequences, and their effects, that law enforcement officials can use to confer deterrence and support forensic investigations. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis installed its second biosensor system to the Department of Homeland Security's National Bioforensic Analysis Center for use in bioforensics.

Epidemiological Surveillance, Infectious Disease Research and Hospital-Associated Infection Control

Ibis and its government partners continue to develop applications for the T5000 Biosensor System to rapidly identify, monitor and control infectious diseases. Specifically, in August 2005, Ibis received a three-year grant worth up to $4.9 million from the NIAID, a part of the NIH. The grant funds the continued development of applications to diagnose infectious diseases and to identify and control hospital-associated infections using the Ibis T5000 Biosensor System. In September 2006, Ibis successfully completed the first phase of this grant and has been granted funding for the second and third phases of the grant, which includes installing an Ibis T5000 Biosensor System at Johns Hopkins University Medical Center. The purpose of the grant is to develop and validate a broad range of respiratory and blood-borne infectious agents, including bacteria and viruses on the NIAID priority list. In addition to deployment of an Ibis T5000, the second and third phases of the grant—approximately $2.6 million—include funding for the purchase of assay kits to analyze human samples in validation studies.

In addition, in September 2003, Ibis received a three-year grant for up to $6 million from the CDC to develop and apply the Ibis biosensor system technology to the surveillance of human infectious disease in the United States. Ibis installed an Ibis biosensor system at the CDC in September 2006 under this contract. Earlier in 2006, Ibis installed a biosensor system at the Naval Health Research Center. The Navy is using the Ibis biosensor system in respiratory disease surveillance and has analyzed hundreds of samples on the Ibis biosensor system at its facility.

Manufacturing

Drug Discovery and Development

In the past, except for small quantities, it was generally expensive and difficult to produce chemically modified oligonucleotides, like the antisense drugs we use in our research and development programs. As a result, we have dedicated significant resources to develop ways to improve manufacturing efficiency and capacity. Since we can use variants of the same nucleotide building blocks and the same type of equipment to produce our oligonucleotide compounds, we found that the same techniques we used to efficiently manufacture one oligonucleotide drug could help improve the manufacturing processes for many other oligonucleotide drugs. By developing several proprietary chemical processes to scale up our manufacturing capabilities, we have greatly reduced the cost of producing oligonucleotide compounds. For example, we have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing our capacity to make the compounds. Through both our internal research and development programs and collaborations with outside vendors we may achieve even greater efficiency and further cost reductions. For example, in November 2004, we and Nitto Denko Corporation announced that we had jointly developed a new high performance solid support for the manufacture of oligonucleotides.

As part of our relationship with Lilly, in 2002 we upgraded and expanded our manufacturing facility, including the addition of a new state-of-the-art manufacturing suite. Lilly provided us with $21.2 million in funding to build the new suite. We can use this facility to manufacture drugs for ourselves and our partners.

Our drug substance manufacturing facility is located in an approximately 28,704 square foot building at 2282 Faraday Avenue, Carlsbad, California. In September 2005, as part of a sale and lease-back transaction, we entered into a lease for this building with an affiliate of BioMed Realty, L.P. The lease has an initial term of fifteen years with an option to extend the lease for up to two five-year periods.

As part of our collaborations we may agree to manufacture clinical trial materials and/or commercial supply for our partners. For example, in the past we have manufactured clinical supply materials for ATL, iCo, Lilly and OncoGenex. We believe we have sufficient manufacturing capacity to meet our current and future obligations under existing agreements with our partners for commercial, research and clinical needs, as well as meet our current internal research and clinical needs. We believe that we have, or will be able to develop or acquire, sufficient supply capacity to meet our anticipated needs. We also believe that with reasonably anticipated benefits from increases in scale and improvements in chemistry, we will be able to manufacture antisense compounds at commercially competitive prices.

Ibis Biosciences, Inc.

We plan to work with partners to manufacture, install and support Ibis T5000 instruments, while we focus on the high-volume, high-margin consumables opportunity through manufacturing and sale of the assay kits and related products.

Ibis recently executed a four-year manufacturing and co-marketing agreement with Bruker Daltonics Inc., a subsidiary of Bruker Biosciences Corporation, to build and install the Ibis T5000 Biosensor System and provide ongoing support to customers beginning in 2007. The Ibis T5000 integrates

Bruker Daltonic's off-the-shelf microTOF™ instrumentation with Ibis' sample processing technology and microbe database. Bruker Daltonics is the exclusive worldwide manufacturer of the Ibis T5000 Biosensor System and is also responsible for order processing, system installations, and service in North America, Europe, and the Middle East. By partnering with a well-established instrumentation company, we can eliminate the duplication of expenses associated with instrument development, manufacture, sales and service, and gain entry into the market much more rapidly than we could on our own.

Ibis intends to manufacture and sell high-volume, high-margin consumables, and has nearly completed building a 1,500 square foot suite dedicated to manufacturing assay kits in its Carlsbad, California facility. We have identified suppliers for raw materials we use to produce quality-controlled ingredients that go into the Ibis T5000 assay kits. Additionally, Ibis has developed quality control and quality assurance standard operating protocols for its assay kits.

Patents and Proprietary Rights

Patents and Proprietary Rights

Our success will depend, in part, on our ability to obtain patent protection for our products in the United States and other countries. We file applications, as appropriate, for patents covering our products and processes. As of March 5, 2007, we owned or exclusively licensed more than 1,500 issued patents worldwide. Patents issued to us, applied for by us or exclusively licensed to us, cover the following types of inventions, processes and products:

- Oligonucleotide chemical modifications covering core chemically-modified oligonucleotide building blocks, and oligonucleotides incorporating the same, which are useful in antisense drug design (including siRNA) as well as other oligonucleotide drugs such as aptamers;
- Antisense drug design, or chemical motifs, covering second generation, including generation 2.2, antisense drug design, including US Patent No. 7,015,315 issued in March of 2006, which protects all of our generation 2.0 or 2.2 antisense compounds until March of 2023;
- Chemical motifs useful in other antisense mechanisms of action, including RNAi and modulation of microRNAs;
- Methods of improving mechanisms of action by which antisense inhibitors inactivate RNA targets using chemically-modified antisense compounds;
- Methods of rapidly identifying antisense compounds targeted to particular RNA target sequences;
- Antisense drug compounds targeted to particular RNA target gene sequences and methods of using these antisense drug compounds to achieve certain therapeutic results;
- Methods of gene functionalization and target validation using antisense compounds;
- Methods for improved oligonucleotide drug manufacture, including processes for large-scale oligonucleotide synthesis;
- Novel formulations for oligonucleotide therapeutics;
- Methods and reagents, covering the Ibis T5000 biosensor system and kits, useful for identifying unknown bioagents (including, but not limited to, bacteria, viruses, fungi and protozoa), including US Patent No. 7,108,874, which issued in September of 2006 and covers the use of the Ibis T5000 to identify unknown bacterial organisms;
- Methods for optimizing the interaction of drug substances with structured RNA target molecules, covering mass spectrometry-based structural activity relationship discovery methods; and

- Anti-infective compounds, including aminoglycosides, derived from our mass spectrometry-based structural-activity relationship discovery methods.

Government Regulation

In addition to regulations enforced by the FDA and those regulations related to our Ibis business discussed below, we are also subject to regulation under the Occupational Safety and Health Act, the Environmental Protection Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act and other present and potential future federal, state and local regulations.

Drug Discovery and Development

Extensive regulation by United States and foreign governmental authorities governs our manufacture and potential sale of therapeutics. In particular, pharmaceutical products are subject to rigorous preclinical and clinical testing and other approval requirements by the FDA in the United States under the Federal Food, Drug and Cosmetic Act and by comparable agencies in most foreign countries. Various federal, state and foreign statutes also govern or influence the manufacture, safety, labeling, storage, record keeping and marketing of such products. State, local, and other authorities also regulate pharmaceutical manufacturing facilities.

In conjunction with obtaining approval of Vitravene, we successfully passed the manufacturing pre-approval inspection by the FDA and European regulatory authorities. Approval of each new drug will require a rigorous manufacturing pre-approval inspection by regulatory authorities.

Ibis Biosciences, Inc.

Ibis' business plan assumes a significant portion of its revenues will come from Ibis T5000 Biosensor Systems and assay kits for *in vitro* diagnostic purposes, whose uses are regulated by the FDA and comparable agencies of other countries. In addition, customers may wish to utilize the Ibis T5000 Biosensor System and assay kits in manners that require additional regulatory approval. To access these markets, Ibis' products may require either premarket approval or 510(k) clearance from the FDA and other regulatory agencies 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 more costly, lengthy, and uncertain and generally takes from six months to two years or longer from submission.

Additionally, we fund our Ibis subsidiary primarily through grants, contracts or subcontracts with agencies of the United States Government. As a result, we must comply with various government regulations, including the Federal Acquisition Regulations (FAR), and agency regulations supplemental to the FAR; the Truth in Negotiations Act, which requires certification and disclosure of all cost and pricing data in connection with certain contract negotiations; and laws, regulations and executive orders restricting the use and dissemination of information classified for national security purposes and the export of certain products and technical data. 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.

Competition

Drug Discovery and Development

For many of their applications, our drugs will compete with existing therapies for market share. In addition, there are a number of companies pursuing the development of oligonucleotide-based technology and the development of pharmaceuticals utilizing this technology. These companies include specialized pharmaceutical firms and large pharmaceutical companies acting either independently or together with biopharmaceutical companies.

Our products under development address numerous markets. The diseases targeted by our drugs for which we may receive regulatory approval will determine our competition. For certain of our products, an important factor in competition may be the timing of market introduction of competitive products. Accordingly, the relative speed with which we can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market are important competitive factors. We expect to compete among products approved for sale based on a variety of factors, including, among other things, product efficacy, safety, reliability, availability, price and patent position.

A number of factors have affected the market for Vitravene, our antisense drug for CMV retinitis. Anti-HIV drugs that were introduced prior to Vitravene's approval have prolonged survival in HIV-infected individuals. This has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections, including CMV retinitis.

Ibis Biosciences, Inc.

While Ibis has a unique technology, the markets for our technologies and products, including biodefense, forensics, epidemiological surveillance, hospital-associated infection control, and IVD, are very competitive, and we expect the intensity of competition to increase. Currently, we compete primarily with companies that are pursuing technologies and products that provide specific detection of individual pathogens requiring a separate test for each pathogen, as opposed to broad identification and strain determination of infectious agents. We are unaware of other technologies that have the ability to do the parallel analysis, quantification, and identification of the bacteria and viruses in a single sample.

Some of the technologies that the Ibis T5000 competes with, including molecular-based approaches, such as real time PCR, bead based techniques, two dimensional arrays, and PCR amplicon sequencing, are being rapidly adopted as new standards in clinical infectious disease diagnostics, although hospitals still rely heavily on traditional culture methods. Emerging molecular-based approaches for the parallel detection of known infectious agents include multiplexed PCR methods and microarray strategies. With the emerging molecular-based methods, prior knowledge and assumptions about the type and strain of bacteria or virus guide the detection strategies, making them less amenable for the high-throughput detection of a broad spectrum of microorganisms or the detection of previously unknown or uncharacterized agents.

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.

Employees

As of March 5, 2007, we employed approximately 274 people, nearly half of whom hold advanced degrees, including 49 people within our Ibis subsidiary. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Collective bargaining agreements do not cover any of our employees, and management considers relations with our employees to be good.

Executive Officers of Isis

The following sets forth certain information regarding our executive officers as of March 5, 2007:

Name	Age	Position
Stanley T. Crooke, M.D., Ph.D .	61	Chairman of the Board, President and Chief Executive Officer
B. Lynne Parshall, J.D.....	51	Director, Executive Vice President, Chief Financial Officer and Secretary
Jeffrey M. Jonas, M.D.....	54	Executive Vice President
C. Frank Bennett, Ph.D	50	Senior Vice President, Research
David J. Ecker, Ph.D.....	52	Vice President, Chief Scientific Officer of Ibis Biosciences, Inc.
Arthur A. Levin, Ph.D.....	53	Senior Vice President, Development
Michael J. Treble	60	Vice President, President of Ibis Biosciences, Inc.
Mark K. Wedel, M.D., J.D.....	60	Senior Vice President, Development and Chief Medical Officer

STANLEY T. CROOKE, M.D., Ph.D.

Chairman of the Board, President and Chief Executive Officer

Dr. Crooke was a founder of Isis and has been Chief Executive Officer and a Director since January 1989. He was elected Chairman of the Board in February 1991. Prior to founding Isis, from 1980 until January 1989, Dr. Crooke was employed by SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories.

B. LYNNE PARSHALL, J.D.

Director, Executive Vice President, Chief Financial Officer, and Secretary

Ms. Parshall has served as a Director of Isis since September 2000. She has served as our Executive Vice President since December 1995, our Chief Financial Officer since June 1994, and our Secretary since November 1991. From February 1993 to December 1995, she was a Senior Vice President of Isis, and from November 1991 to February 1993, she was a Vice President of Isis. Prior to joining Isis, Ms. Parshall practiced law at Cooley Godward LLP (now Cooley Godward Kronish LLP), outside counsel to Isis, where she was a partner from 1986 to 1991. Ms. Parshall is on the Board of Trustees of the Bishops School and is also a member of the American, California and San Diego bar associations. Ms. Parshall has served on the Board of Corautus Genetics Inc. since May 2005 and of CardioDynamics International Corp. since June 2005, both of which are biopharmaceutical companies.

JEFFREY M. JONAS, M.D.

Executive Vice President

Dr. Jonas joined Isis as Executive Vice President in February 2007. He leads Clinical Development, Preclinical Development, Regulatory Affairs, and Quality Assurance and Compliance at Isis. Prior to joining Isis Pharmaceuticals, Dr. Jonas was Chief Medical Officer and Executive Vice President at Forest Laboratories, Inc., responsible for Clinical Development, Medical Affairs, Pharmacovigilence, Regulatory Affairs, Health Economics, and External Scientific Affairs. Dr. Jonas' initial experience in the pharmaceutical industry began in 1991 at Upjohn Laboratories initially as Director of Psychopharmacology and after several promotions ultimately as Chief Medical Officer and VP, Clinical Development.

C. FRANK BENNETT, Ph.D.

Senior Vice President, Research

Dr. Bennett was promoted to Senior Vice President, Research in January 2006. From June 1995 to January 2006, Dr. Bennett served as our Vice President, Research. From March 1993 to June 1995, he was Director, Molecular Pharmacology, and from May 1992 to March 1993, he was an Associate Director in our Molecular and Cellular Biology department. Prior to joining Isis in 1989, Dr. Bennett was employed by SmithKline and French Laboratories in various research positions. He serves as a Director of Antisense Therapeutics Ltd., a biopharmaceutical company.

DAVID J. ECKER, Ph.D.

Vice President, Chief Scientific Officer of Ibis Biosciences, Inc.

Dr. Ecker was a founder of Isis and has served as a Vice President since June 1995. In 2001, he assumed the role of Scientific Head of our Ibis Biosciences subsidiary and is currently serving as its Chief Scientific Officer. He served as our Vice President, Biology from July 1993 to June 1995, as our Executive Director, Molecular and Cellular Biology from February 1993 to July 1993, and as our Director, Molecular and Cellular Biology from February 1989 to February 1993. From 1984 until February 1989, he was employed by SmithKline and French Laboratories in a variety of research positions.

ARTHUR A. LEVIN, Ph.D.

Senior Vice President, Development

Dr. Levin was promoted to Senior Vice President, Development in January 2006. From 1995 until January 2006 he served as our Vice President, Development. Prior to joining Isis, Dr. Levin worked at Hoffmann-La Roche Inc. where he was Research Leader in their Investigative Toxicology Department managing the Nuclear Receptor Research Group. During his tenure at Hoffman-LaRoche, Dr. Levin also established and supervised laboratories dedicated to the research of mechanisms of toxicity, biochemical toxicology and toxicokinetics.

MICHAEL J. TREBLE

Vice President, President of Ibis Biosciences, Inc.

Mr. Treble joined Isis in December 2004 as President of our Ibis Biosciences subsidiary and a Vice President of the Company. Prior to joining Isis, Mr. Treble was President and Chief Executive Officer from 2000 to 2003 of Nimblegen System, Inc., which develops DNA micro array and chemistry technologies. From 1995 to 2000, Mr. Treble was the Executive Vice President, Chief Operating Officer and Director of Third Wave Technologies, Inc. which provides research and molecular diagnostic products to the healthcare industry. Mr. Treble was also the Chairman, Chief Executive Officer and founder of Genetic Models, Inc. from 1991 until it was sold to Charles River Laboratories in July 2001.

MARK K. WEDEL, M.D, J.D.

Senior Vice President, Development and Chief Medical Officer

Dr. Wedel joined Isis in 2001 and is responsible for clinical operations, strategic therapeutic portfolio management, and oversees all of Isis' development programs. Prior to joining Isis, he served as Director of Medical Affairs, Director of Pulmonary Therapeutics, and as a consultant for the U.S. Department of Justice in its Health Care Fraud Division. Prior to that, Dr. Wedel was the Medical Director of the Medical/Surgical Intensive Care Unit, Green Hospital of the Scripps Clinic and Research Foundation and the Attending Intensivist, responsible for the care and treatment of critically ill patients.

Item 1A. RISK FACTORS

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

Risks 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 December 31, 2006, we had accumulated losses of approximately $816.8 million and stockholders' equity of approximately $68.6 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 research grants and the sale or licensing of patents as well as interest income. We currently have only one product, Vitravene, approved for commercial use. This product has limited sales potential, Novartis, and our exclusive distribution partner for this product no longer markets it. 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 drugs are undergoing clinical trials or are in the early stages of research and development. All of our drugs 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 second half of 2010. 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, as in our transaction with Symphony GenIsis, we may obtain funds through arrangements with collaborative partners or others, which could require us to give up rights to certain of our technologies, drugs or products.

Since corporate partnering is a key part of our strategy to fund the development and commercialization of our development programs, if any of our collaborative partners fail to fund our collaborative programs, 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, including our two lead products ISIS 301012 and ISIS 113715. However, we may not be able to negotiate additional attractive collaborative arrangements.

Many of the drugs in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics Limited, iCo Therapeutics, Inc., ImQuest Pharmaceuticals, Inc., Merck & Co., Inc., OncoGenex Technologies Inc. and Lilly. If any of these pharmaceutical companies 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.

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 disappointing results of the Phase 3 clinical trials, Lilly discontinued its investment in Affinitak.

In addition, the disappointing results of the two Affinitak clinical trials, our Phase 3 clinical trials of alicaforsen in patients with active Crohn's disease, or any future clinical trials 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.

Even with funding from corporate partners, if our partners do not effectively perform their obligations under our agreements with them, it would delay or stop the progress of our product development programs.

In addition to receiving funding, we enter into collaborative arrangements with third parties to:

- conduct clinical trials;
- seek and obtain regulatory approvals; and
- manufacture, market and sell existing and future products.

Once we have secured a collaborative arrangement to further develop and commercialize one of our development programs, these collaborations may not continue or result in commercialized drugs, or may not progress as quickly as we anticipated.

For example, a collaborator could determine that it is in its financial interest to:

- pursue alternative technologies or develop alternative products that may be competitive with the product that is part of the collaboration with us;
- pursue higher-priority programs or change the focus of its own development programs; or
- choose to devote fewer resources to our drugs than it does for drugs of its own development.

If any of these occur, it could affect our partner's commitment to the collaboration with us and could delay or otherwise negatively affect the commercialization of our drugs.

If we cannot protect our patents or our other proprietary rights, others may compete more effectively 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.

In addition, our Ibis business relies in part on trade secret laws and nondisclosure, confidentiality and other agreements to protect some of the proprietary technology that is part of the Ibis T5000 Biosensor System. However, these laws and agreements may not be enforceable or may not provide meaningful protection for Ibis' trade secrets or other proprietary information in the event of unauthorized use or disclosure or other breaches of these agreements.

To date, virtually all of Ibis' research and development activities have been funded under contracts from the U.S. government (either directly or through subcontracts from prime contractors or higher-tier subcontractors). As a general matter, subject to certain disclosure, notice, filing, acknowledgement and reporting obligations, Ibis is entitled to retain title to any inventions conceived or first reduced to practice under government contracts, but the government will have a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced these inventions for or on behalf of the United States.

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.

For example, in December 2006, the European Patent Office (EPO) Technical Board of Appeal reinstated with amended claims our Patent EP0618925 which claims a class of antisense compounds, any of which is designed to have a sequence of phosphorothioate-linked nucleotides having two regions of chemically modified RNA flanking a region of DNA. Prior to its reinstatement, this patent was originally opposed by several parties and revoked by an EPO Opposition Division in December of 2003. We intend to fully exercise our rights under this patent by pursuing licensing arrangements, but if licensing efforts are unsuccessful we may choose to assert our rights through litigation.

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 and may disclose the timing of a variety of clinical, regulatory and other milestones, such as when we anticipate a certain drug will enter the clinic, when we anticipate completing a clinical trial, or when we anticipate filing an application for marketing approval. We base our estimates on present facts and a variety of assumptions. Many underlying assumption are outside of our control. If we do not achieve milestones in accordance with our or investors' expectations, 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 that would prevent them from leaving Isis. 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. In addition, 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 December 31, 2006, the market price of our common stock ranged from $5.09 to $14.00 per share. On March 5, 2007, the closing price of our common stock on the Nasdaq Global Market was $8.37. 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.

Because we use biological materials, hazardous materials, chemicals and radioactive compounds, if we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research, development and manufacturing activities involve the use of potentially harmful biological materials as well as materials, chemicals and various radioactive compounds that could be

hazardous to human health and safety or the environment. These materials and various wastes resulting from their use are stored at our facilities in Carlsbad, California pending ultimate use and disposal. We cannot completely eliminate the risk of contamination, which could cause:

- interruption of our research, development and manufacturing efforts;
- injury to our employees and others;
- environmental damage resulting in costly clean up; and
- liabilities under federal, state and local laws and regulations governing health and human safety, as well as the use, storage, handling and disposal of these materials and resultant waste products.

In such an event, we may be held liable for any resulting damages, and any such liability could exceed our resources. Although we carry insurance in amounts and type that we consider commercially reasonable, we do not have insurance coverage for losses relating to an interruption of our research, development or manufacturing efforts caused by contamination, and we cannot be certain that the coverage or coverage limits of our insurance policies will be adequate. In the event our losses exceed our insurance coverage, our financial condition would be adversely affected.

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, fires and acts of terrorism, 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.

In addition, the provisions of our convertible subordinated notes could make it more difficult or more expensive for a third party to acquire us. Upon the occurrence of certain transactions constituting a fundamental change, holders of the notes will have the right, at their option, to require us to repurchase all of their notes or a portion of their notes, which may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over the then current market prices.

Future sales of our common stock in the public market could adversely affect the trading price of our securities.

Future sales of substantial amounts of our common stock in the public market, or the perception that such sales could occur, could adversely affect trading prices of our securities. We have granted registration rights to Lilly, which cover approximately 2.5 million shares of our common stock, which we issued to Lilly upon the conversion of outstanding convertible securities. 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 warrants we issued as part of our August 2005 private placement as well as 4.25 million shares of our common stock issuable upon the exercise of the warrant we issued to Symphony GenIsis Holdings. 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. Finally, we have granted registration rights to the holders of our 2⅝% convertible subordinated notes that include the approximately 11,111,116 shares issuable upon conversion of the notes. The addition of any of these shares into the market may have an adverse effect on the price of our securities.

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

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 Market. 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 drugs, 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, including ISIS 301012 and ISIS 113715, before a drug can be approved for sale. We must conduct these trials in compliance with FDA 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, including ISIS 301012 and ISIS 113715, 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, including ISIS 301012 and ISIS 113715. Failure to receive these approvals or delays in these approvals could prevent or delay commercial introduction of a product, including ISIS 301012 and ISIS 113715, 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, including ISIS 301012 and ISIS 113715, 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 we may need to abandon one or more of our drug development programs.

Drug discovery and development has inherent risks and the historical failure rate for drugs is high. Antisense technology in particular is relatively new and unproven. If we cannot demonstrate that our drugs, including ISIS 301012 and ISIS 113715, are safe and effective drugs for human use, we may need to abandon one or more of our drug development programs.

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 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 clinical 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.

Even if our drugs are successful in preclinical and early human clinical studies, these results do not guarantee these drugs will be successful in late-stage clinical trials.

Successful results in preclinical or early human clinical trials, including the recently announced Phase 2 results for ISIS 301012 and ISIS 113715, may not predict the results of late-stage clinical trials. There are a number of factors that could cause a clinical trial to fail or be delayed, including:

- the clinical trial may produce negative or inconclusive results;
- regulators may require that we hold, suspend or terminate clinical research for noncompliance with regulatory requirements;
- we, our partners, the FDA or foreign regulatory authorities could suspend or terminate a clinical trial due to adverse side effects of a drug on subjects or patients in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials;
- enrollment in our clinical trials may be slower than we currently anticipate;
- the cost of our clinical trials may be greater than we anticipate; and
- the supply or quality of our drugs or other materials necessary to conduct our clinical trials may be insufficient, inadequate or delayed.

Any failure or delay in one of our clinical trials, including our Phase 2 development programs for ISIS 301012 and ISIS 113715, could reduce the commercial viability of our drugs, including ISIS 301012 and ISIS 113715.

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, ISIS 325568 and ISIS 377131 unless we exercise our option to acquire all of these drugs 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 prior to its expiration.

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 a five-year warrant to purchase shares of our common stock we issued to Symphony GenIsis, 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, ISIS 325568 and ISIS 377131. 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 purchase 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 option prior to its expiration, we will lose our rights in our apoB-100, GCGR, and GCCR programs. We may not have the financial resources to exercise the purchase 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 option.

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

We have licensed to Symphony GenIsis our intellectual property rights, including commercialization rights, to our drugs 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 drugs 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 drugs 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 payors accepting our products as medically useful, cost-effective and safe. We cannot guarantee that, if approved for commercialization, doctors will use our products to treat patients. We currently have one commercially

available 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 payors.

Based on the profile of our drugs, physicians, patients, patient advocates, payors 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 or prevent 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 that are:

- priced lower than our drugs;
- safer than our drugs; or
- more effective than our drugs.

These competitive developments could make our products obsolete or non-competitive.

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 drugs and, as a result, could delay or otherwise negatively affect the commercialization of our drugs.

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 drugs 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 drugs and expect to continue to do so in the future. For example, Medpace is the primary clinical research organization for clinical trials for ISIS 301012. 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 or a termination of our relationship with these third parties could delay or prevent the development, approval and commercialization of our drugs, including ISIS 301012.

Risks Associated With Our Ibis Biosciences Business

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 continued research and development to achieve our business objectives. For Ibis to be commercially successful, we must convince potential customers that our Ibis T5000 Biosensor System is an attractive alternative to existing methods of identifying pathogens. 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 may not recover our investment in this technology and our Ibis T5000 Biosensor System business could fail to meet our business and financial objectives.

If we fail to sell the Ibis T5000 Biosensor System to a minimum customer base, our ability to generate revenues from sales of assay kits will be negatively affected.

A key element of our business plan for Ibis calls for us to deploy the Ibis T5000 Biosensor System to a broad customer base. If we cannot create a broad installed base of our Ibis T5000 Biosensor System, our ability to sell assay kits, the consumables used to operate the system, may be significantly and adversely affected. Even if we successfully achieve broad installation of the Ibis T5000 Biosensor System, customers may not perform as many analyses as we anticipate, which may affect the assumptions underlying our business plan for Ibis and lead to lower-than-expected revenues.

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

In July 2006, we entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker Daltonics 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 Daltonics 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 Daltonics to successfully manufacture and distribute our Ibis T5000 Biosensor System, but do not control many aspects of Bruker Daltonics activities. If Bruker Daltonics 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 or financial 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 Daltonics, 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. Specifically, Ibis expects to depend on third parties to sell and distribute its assay kits to non-government customers in the healthcare-associated infection control and infectious disease diagnostic markets. We may not successfully establish a relationship in these markets or be able to make alternative arrangements. If we are unable to reach agreements with suitable commercial or financial partners, we may fail to meet our business objectives for the Ibis T5000 Biosensor System. 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 instruments and related assay kits.

We depend on government contracts for most of Ibis' 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.

Virtually all of Ibis' revenues are from the sale of services and products to the U.S. 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, even if we have fully performed our obligations. Since a large portion of Ibis' government contracts are milestone based, if Ibis fails to meet a specific milestone within the specified delivery date, our government partner may be more likely to reduce or cancel its contract with Ibis. Our revenues and cash flows from U.S. government contracts could also be reduced by declines in U.S. defense, homeland security and other federal agency budgets.

For the three months and year ended December 31, 2006, we derived approximately 13% and 37%, respectively, of our revenue from agencies of the U.S. 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 U.S. government contracts and subcontracts are simultaneously delayed or canceled for budgetary, performance or other reasons.

If U.S. 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 U.S. 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 Ibis. 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 Ibis fails to compete effectively, it may not succeed or contribute significant revenues.

The market for products such as Ibis' 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. To remain competitive, we will need to continually improve Ibis' products so that, when compared to alternatives, its products:

- provide faster results;
- are cost-effective;
- deliver more accurate information;
- are more user friendly; and

- support a broad range of applications.

If Ibis cannot keep its products ahead of its competitors in these areas, Ibis' revenues will suffer and we may not meet our commercialization goals.

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.

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

We expect to derive a significant portion of our Ibis 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 Biosensor System internationally are subject to additional risks that could negatively affect our operating results.

Our success will depend in part on our ability and Bruker's ability to market and sell the Ibis T5000 Biosensor System 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 or at all, 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, we may not successfully obtain approval.

Ibis' business plan assumes a significant portion of its revenues will come from Ibis T5000 Biosensor Systems and assay kits for *in vitro* diagnostic purposes, whose uses are regulated by the FDA and comparable agencies of other countries. In addition, customers may wish to utilize the Ibis T5000 Biosensor System and assay kits in manners that require additional regulatory approval. To access these markets, Ibis' products may require either premarket approval or 510(k) clearance from the FDA and other regulatory agencies 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, and 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 clinical trials do not necessarily predict final results, and acceptable results in early clinical trials may not be repeated in later clinical 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. If our Ibis T5000 Biosensor System is considered a medical device, after gaining market approval from the FDA, our Ibis T5000 Biosensor System may be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, recordkeeping and reporting of safety and other post-market information.

If we become subject to product liability claims relating to Ibis, we may be required to pay damages that exceed our insurance coverage.

Any product liability claim brought against us with respect to Ibis, with or without merit, could result in the increase of our product liability insurance rates or the inability to secure coverage in the future. Expenses incurred by our insurance provider in defending these claims will reduce funds available to settle claims or pay adverse judgments. In addition, we could be liable for amounts in excess of policy limits, which would have to be paid out of our cash reserves, and our cash reserves may be insufficient to satisfy the liability. Finally, even a meritless or unsuccessful product liability claim could harm Ibis' reputation in the industry, lead to significant legal fees, and could result in the diversion of management's attention from managing our business.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties.

As of March 5, 2007, we occupied approximately 130,600 square feet of laboratory and office space, including 6,900 square feet of manufacturing area for our drug development business built to meet Good Manufacturing Practices and 12,900 square feet, which our Ibis subsidiary occupies, including 1,500 square feet of manufacturing for Ibis' assay kits. We are located in three buildings in Carlsbad, California. We lease all of these buildings under lease agreements. The lease for the building that houses our Ibis business will expire in 2010 and has two five-year options to extend the lease. The lease on the building we primarily use for laboratory and office space for our drug development business will expire in 2012 and has a five-year option to extend the lease. The lease on the building we primarily use for our drug development manufacturing will expire in 2020 and has two five-year options to extend the lease.

Item 3. 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 purports to license 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, we and Ajinomoto entered into a Settlement and Non-Exclusive License Agreement. Accordingly, we recorded a $418,000 charge, which represents the present value of our liability under this agreement.

Item 4. Submission of Matters to a Vote of Security Holders.

Not applicable.

PART II

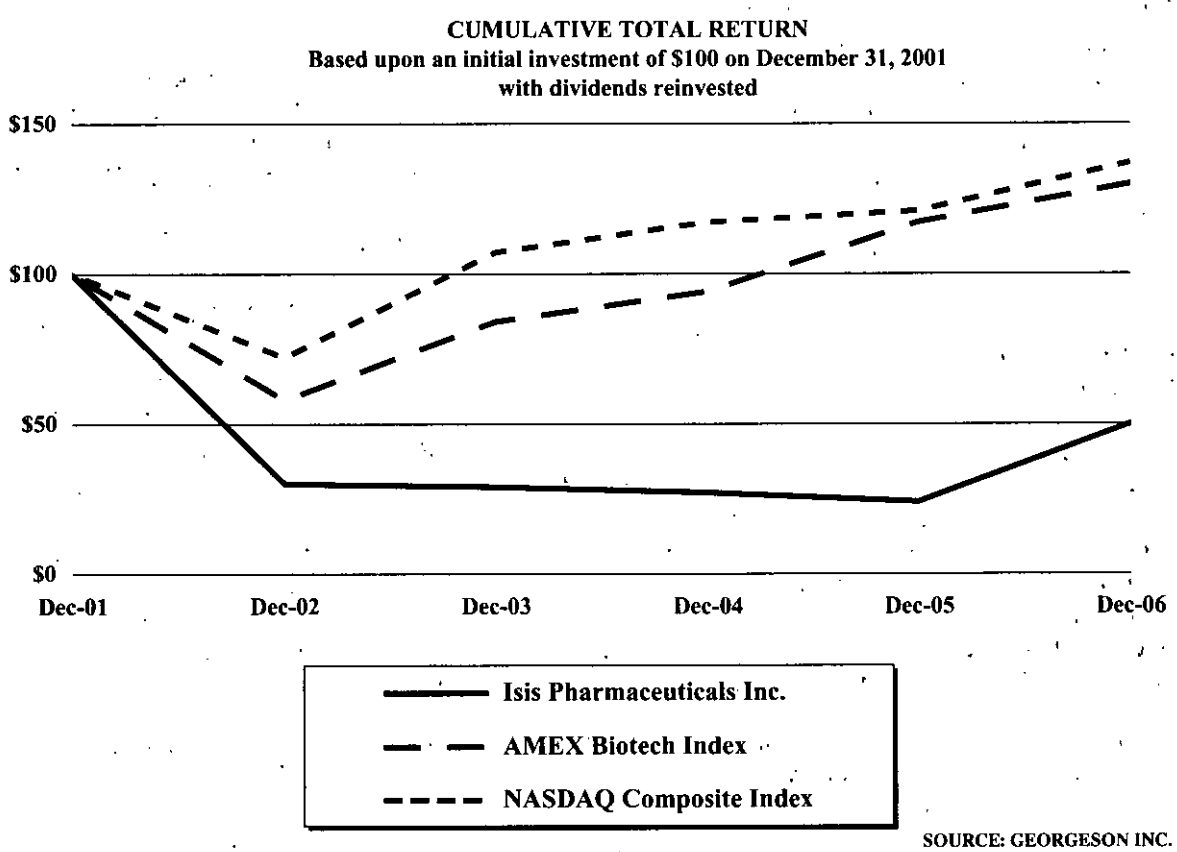
Item 5. Market for Registrant's Common Equity and Related Stockholder Matters and Issuer Repurchases of Equity Securities

Our common stock is traded publicly through the Nasdaq Global Market under the symbol "ISIS." The following table presents quarterly information on the price range of our common stock. This information indicates the high and low sale prices reported by the Nasdaq Global Market. These prices do not include retail markups, markdowns or commissions.

	HIGH	LOW
2006		
First Quarter	$9.34	$5.09
Second Quarter	$9.50	$5.76
Third Quarter	$7.89	$5.57
Fourth Quarter	$14.0	$7.06
2005		
First Quarter	$6.09	$3.76
Second Quarter	$4.29	$2.76
Third Quarter	$5.80	$3.75
Fourth Quarter	$5.41	$4.20

As of March 5, 2007, there were approximately 960 stockholders of record of our common stock. We have never paid dividends and do not anticipate paying any dividends in the foreseeable future.

Set forth below is a table and chart comparing the total return on an indexed basis of $100 invested on December 31, 2001 in our common stock, the NASDAQ Composite Index (total return) and the AMEX Biotech Index. The total return assumes reinvestment of dividends.



SOURCE: GEORGESON INC.

	Dec-01	Dec-02	Dec-03	Dec-04	Dec-05	Dec-06
Isis Pharmaceuticals Inc.	$100	$30	$ 29	$ 27	$ 24	$ 50
AMEX Biotech Index.....	$100	$58	$ 84	$ 94	$117	$130
NASDAQ Composite Index ...	$100	$72	$107	$117	$121	$137

Item 6. Selected Consolidated Financial Data (in thousands, except per share amounts):

	Years Ended December 31,				
	2006	2005	2004	2003	2002
Consolidated Statement of Operations Data:					
Revenue (includes amounts for R&D, licensing and royalties)	$ 24,532	$ 40,133	$ 42,624	$ 49,990	$ 80,179
Research and development expenses	$ 80,567	$ 82,467	$ 118,474	$116,963	$124,074
Net loss applicable to common stock(1)	$(45,903)	$(72,401)	$(142,864)	$ (95,690)	$ (73,302)
Basic and diluted net loss per share	$ (0.62)	$ (1.15)	$ (2.52)	$ (1.73)	$ (1.35)
Shares used in computing basic and diluted net loss per share	74,308	62,877	56,642	55,463	54,480

	Years Ended December 31,				
	2006	2005	2004	2003	2002
Consolidated Balance Sheet:(2)					
Cash, cash equivalents and short-term investments	$ 193,333	$ 94,389	$ 103,883	$ 215,504	$ 289,353
Working capital	$ 181,064	$ 82,065	$ 82,193	$ 194,004	$ 244,230
Total assets	$ 255,907	$ 166,373	$ 208,425	$ 334,942	$ 438,683
Long-term debt, capital lease and other obligations, less current portion	$ 132,866	$ 139,915	$ 236,611	$ 213,397	$ 192,893
Noncontrolling interest in Symphony GenIsis, Inc	$ 29,339	$ —	$ —	$ —	$ —
Accumulated deficit	$(816,751)	$(770,848)	$(698,447)	$(555,583)	$(459,893)
Stockholders' equity (deficit)	$ 68,563	$ 2,665	$ (72,133)	$ 67,178	$ 155,477

(1) Our net loss applicable to common stock includes charges (benefit) related to restructuring activities of ($536,000), $7.0 million, $32.4 million, $1.8 million, and $1.4 million in 2006, 2005, 2004, 2003, and 2002, respectively.

(2) In January 2007, we completed a $162.5 million convertible debt offering which matures in 2027 and bears interest at 2⅝%. We intend to use the net proceeds to repurchase our existing 5½% convertible subordinated notes. Through privately negotiated transactions, we have already repurchased approximately $44.1 million aggregate principal amount of the total outstanding of our 5½% convertible notes.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

Overview

We are a biopharmaceutical company that, since our inception in 1989, has pioneered the science of antisense for the development of a new class of drugs to treat important diseases. We are the leader in making drugs that target RNA, and we have a strong proprietary position in RNA-based drug discovery technologies. With our primary technology, antisense, we create inhibitors, called oligonucleotides, designed to hybridize, with a high degree of specificity to their RNA target and modulate the production of specific proteins associated with disease. Separately, within our Ibis Biosciences subsidiary, we have developed a revolutionary biosensor system, called the Ibis T5000 Biosensor System, that can simultaneously identify from a sample a broad range of infectious organisms without needing to know beforehand what might be present in the sample.

We have a broad patent portfolio covering our technologies. We own or exclusively license more than 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 December 31, 2006, we had generated more than $77 million from our intellectual property licensing program that helps support our internal drug discovery and development programs, including more than $10 million in 2006 from licensing activities through our agreements with Alnylam Pharmaceuticals, Inc., Merck & Co., Inc., Pfizer, Inc., iCo Therapeutics, Inc., and Drug Royalty USA, Inc.

In addition to the important progress we and our partners made with our second generation drugs in development and the achievements of our Ibis subsidiary in commercializing the Ibis T5000 Biosensor System, we completed three important transactions that continued our successful efforts to strengthen our balance sheet. First, in April 2006, we entered into a $75 million collaboration with Symphony GenIsis, Inc. to fund development of ISIS 301012 and two new diabetes drugs. Additionally, during the second half of 2006, we drew down the entire $75 million under our equity line with Azimuth Opportunity Ltd. by issuing approximately 8.0 million shares of our common stock resulting in net proceeds to us of $74.9 million. Most recently, in January 2007, we issued $162.5 million of 2⅝% convertible subordinated notes due 2027. Concurrent with this financing we repurchased approximately $44.1 million of the total amount outstanding of our 5½% convertible subordinated notes due 2009 and we intend to use a portion of the remaining net proceeds from this offering to repurchase the remaining 5½% notes. The significantly reduced interest rate of the 2⅝% notes compared to the 5½% notes reduces our annual cash interest payments by approximately $2.6 million. In addition, the extended maturity date of the 2⅝% notes compared to the 5½% notes further strengthens our balance sheet. The Symphony GenIsis collaboration, the Azimuth Opportunity transaction and the issuance of the 2⅝% notes provide us with the financial strength to continue to successfully execute our goals.

Business Segments

We focus our business on two principal segments:

Drug Discovery and Development—Within our primary business segment, we are exploiting our expertise in RNA to discover and develop novel drugs for our product pipeline and for that of our partners. We have successfully commercialized the world's first antisense drug and, along with our partners, we currently have 17 drugs in development. Our partners are licensed to develop, with our support, eleven of these 17 drugs, which substantially reduces our development costs. We focus our internal drug development programs on drugs to treat cardiovascular, metabolic and inflammatory diseases. Our partners focus on disease areas such as ocular, viral, inflammatory and neurodegenerative diseases, and cancer.

Ibis Biosciences—Ibis Biosciences, Inc., formerly a division of Isis and now a wholly owned subsidiary of Isis, has developed a revolutionary biosensor system, called 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. We are commercializing the Ibis T5000 Biosensor System and related assay kits for use in biodefense, forensics, epidemiological surveillance, infectious disease research, hospital-associated infection control and plan to commercialize the Ibis T5000 Biosensor System for use in *in vitro* diagnostics.

Much of the development of the Ibis T5000 Biosensor System and related applications has been funded through U.S. government contracts and grants. As of December 31, 2006, we had earned $57.5 million in revenue since inception from numerous government agencies. In addition, we have an additional $7.3 million committed under our existing contracts and grants.

Critical Accounting Policies

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

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

Descriptions of these critical accounting policies follow.

Revenue Recognition

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

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

We often enter into collaborations where we receive non-refundable upfront payments for prior or future expenditures. We recognize revenue related to upfront payments ratably over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligations when the agreements we enter into do not clearly define such information. Should different estimates prevail, revenue recognized

could be materially different. We have made estimates of our continuing obligations on several agreements, including our collaborations with Antisense Therapeutics Ltd., Lilly, OncoGenex and Pfizer.

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

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

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

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

In the fourth quarter of 2006, we sold our first commercial Ibis T5000 Biosensor System. The sale of an Ibis T5000 Biosensor System contains multiple elements. Since we have no previous experience of commercially selling the Ibis T5000 Biosensor System, we have no basis to determine the fair values of the various elements included in the system; therefore, we must account for the entire system as one deliverable and recognize revenue over the entire period of performance. For a one-year period following the sale, we have ongoing support obligations for the Ibis T5000 Biosensor System, therefore we are amortizing the revenue for the entire system over a one-year period. Once we obtain a sufficient number of sales to enable us to identify each element's fair value, we will be able to recognize revenue separately for each element.

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

Valuation of Investments in Marketable Securities

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

In addition to our investments in marketable securities, we have equity investments in privately- and publicly-held biotechnology companies. We hold ownership interests of less than 20% in each of the respective entities. In determining if and when a decrease in market value below our cost in our equity positions is other-than-temporary, we examine historical trends in the stock price, the financial condition of the issuer, near term prospects of the issuer, and our current need for cash. When we determine that a decline in value is other-than-temporary, we recognize an impairment loss in the period in which the other-than-temporary decline occurs. During the second quarter of 2006, we recorded a net gain on investments. This net gain on investments represented a gain of $2.7 million realized on the sale of a portion of the equity securities of Alnylam that we own, partially offset by a non-cash loss on investment of $465,000 related to the impairment of our equity investment in ATL, which we believe was primarily a result of the financial market conditions related to biotechnology companies at that time. In the second half of 2006, we recorded a net unrealized gain of $390,000 related to our equity investment in ATL as a separate component of stockholders' equity. This reflected the increase in the market value of the investment since the impairment in the second quarter of 2006. We did not record an impairment loss on our investments in 2005. During 2004, we recorded a non-cash loss on investments of $5.1 million, principally related to the impairment of our equity investment in Alnylam.

Valuation of Long-Lived Assets

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

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

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

to our current focus. We had additional write-downs of $15.6 million in 2005 associated with our restructuring activities, which were primarily related to the sale of three of our buildings. In 2006, we incurred charges of $2.4 million primarily related to the write-down of equipment and patent costs that were non-essential to our current focus.

Valuation of Inventory

We include in inventory raw material costs and related manufacturing costs for drugs that we manufacture for our partners under contractual terms and that we use primarily in our clinical development activities and drug products. We expense these costs when we deliver our drugs to partners, or as we use these drugs in our own clinical trials. Also included in inventory, as of December 31, 2006, are material costs and related manufacturing costs associated with our Ibis T5000 Biosensor System. We reflect our inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. We review inventory periodically and reduce our carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. We consider several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for our drugs and clinical trial materials and historical write-offs. In the fourth quarter of 2004, we recorded a charge of approximately $21.0 million for the write-down of inventory to its net realizable value related to our decision to focus our resources on key programs.

Estimated Liability for Clinical Development Costs

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

Valuation Allowance for Net Deferred Tax Assets

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

Segment Information

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

Stock-Based Compensation

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

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

We utilize the Black-Scholes model and assumptions discussed in Note 4 for estimating the fair value of the stock-based awards we granted. Compensation expense for all stock-based payment awards is recognized using the accelerated multiple-option approach. Under the accelerated multiple-option approach (also known as the graded-vesting method), an entity recognizes compensation expense over the requisite service period for each separately vesting tranche of the award as though the award were in substance multiple awards, which results in the expense being front-loaded over the vesting period. Our risk-free interest rate assumption is based upon observed interest rates appropriate for the term of our employee stock options and our ESPP. The dividend yield assumption is based on our history and expectation of dividend payouts. We have not paid dividends in the past and do not expect to in the future. We use a weighted average of the historical stock price volatility of our stock to calculate the expected volatility assumption required for the Black-Scholes model consistent with SFAS 123R. The expected term of stock options granted represents the period of time that they are expected to be outstanding. For our 2002 Non-Employee Directors' Stock Option Plan, we estimate the expected term of options granted based on historical exercise patterns. For our employee stock option plans, the estimated expected term is a derived output of the simplified method, as allowed under SAB 107. We estimated forfeitures based on historical experience. 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

Years Ended December 31, 2006 and December 31, 2005

Revenue

Total revenue for the year ended December 31, 2006 was $24.5 million, compared to $40.1 million for 2005. The decrease in revenue for 2006 compared to 2005 was primarily due to a decrease in revenue associated with our collaboration with Lilly. This ongoing collaboration was extended in August 2005 to focus on a select number of targets and as a result is no longer a source of significant revenue. Our revenue fluctuates based on the timing of activities under agreements with our partners. For example, we earned revenue in 2006 of $750,000 compared to revenue of $3.7 million in 2005 from Alnylam when they sublicensed our technology to pharmaceutical partners for the development of RNAi therapeutics. In 2006 and 2005, in accordance with agreed upon timing, we also earned $8.0 million and $7.0 million, respectively, of revenue from Drug Royalty USA, Inc., as partial payment for the acquisition of a part of

our royalty rights in Macugen. In addition, our Ibis revenue was lower in 2006 than in 2005 as described below under "Ibis Biosciences, Inc." Our ability to maintain revenue at current levels will depend on our ability to obtain new revenue sources and expand existing revenue sources in 2007.

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

	Year Ended December 31,	
	2006	2005
Drug Discovery and Development:		
Research and development revenue	$ 5,418	$16,817
Licensing and royalty revenue	9,441	11,523
	$14,859	$28,340
Ibis Biosciences:		
Research and development revenue	$ 9,117	$11,793
Commercial revenue (1)	556	—
	$ 9,673	$11,793
Total revenue:		
Research and development revenue	$14,535	$28,610
Commercial revenue (1)	556	—
Licensing and royalty revenue	9,441	11,523
	$24,532	$40,133

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

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Revenue for our drug discovery and development segment includes revenue from research and development under collaborative agreements and licensing and royalty revenue. Our revenue under the category of research and development revenue under collaborative agreements for the year ended December 31, 2006 was $5.4 million, compared to $16.8 million for 2005. The decrease of $11.4 million was primarily due to a decrease in revenue associated with our collaboration with Lilly.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was $9.4 million for the year ended December 31, 2006, compared to $11.5 million for 2005. We earned revenue in 2006 of $750,000 and revenue of $3.7 million in 2005 from Alnylam when Alnylam sublicensed our technology to pharmaceutical partners for the development of RNAi therapeutics. In addition, in 2006 and 2005, in accordance with agreed upon timing, we earned $8.0 million and $7.0 million, respectively, from Drug Royalty USA, Inc., as partial payment for the acquisition of a part of our royalty rights in Macugen.

Ibis Biosciences, Inc.

During 2006, Ibis achieved important milestones in implementing its commercial plan, including receiving its first commercial order for two Ibis T5000 Biosensor Systems, one of which was delivered in late 2006 and the second of which Ibis expects to deliver early in 2007. Additionally, in 2006, Ibis received a contract worth up to $1.9 million to analyze samples in its assay services laboratory. As a result of these achievements, Ibis earned commercial revenue of $556,000. Because Ibis provides a full year of support for

each Ibis T5000 Biosensor System following installation, Ibis is amortizing the revenue for each instrument sold over the period of this support obligation.

To develop the Ibis T5000 Biosensor System and related assay kits, Ibis receives contracts and grants from U.S. government agencies. Ibis generated revenue from its government contracts and grants of $9.1 million for 2006 compared to $11.8 million for 2005. Ibis' revenue from government contracts fluctuates based on when the contracts are awarded, the period of performance for the contracts, the funding amount of the contracts, the labor rates applicable to the activities under the contracts and the timing and type of these activities. For example, in 2006, two large government contracts that were active in 2005 ended and were replaced with several new but smaller contracts, resulting in reduced revenue in 2006 compared to 2005. Additionally, the average labor rate that Ibis charged its government partners in 2006 was lower than in 2005, which also contributed to Ibis' reduced revenue in 2006 compared to 2005. During the fourth quarter of 2006, Ibis announced that it had successfully completed the first phase of its Challenge Grant from the NIAID, a part of the NIH, and had 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 2007.

We receive our funding from DARPA through a subcontract with San Diego-based Science Applications International Corporation. Historically, we have generated the majority of our government-funded revenue through our collaboration with SAIC. This collaboration accounted for approximately 8% and 14% of our total revenue in the years ended 2006 and 2005, respectively, which represents 20% and 48% of our 2006 and 2005 Ibis revenue, respectively. In the future, we expect the percentage of revenue from SAIC to continue to decrease as we continue to obtain additional contracts from other government agencies.

From inception through December 31, 2006, Ibis has earned $57.5 million in revenue from various government agencies to further the development of our Ibis T5000 Biosensor System and related assay kits. An additional $7.3 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 were $92.7 million and $97.3 million for the years ended December 31, 2006 and 2005, respectively. The decrease in operating expenses, which was principally a result of cost savings achieved through the increased focus on our key programs, led to a decrease of $4.6 million in our operating expenses in 2006, which included compensation related to stock options for 2006 of $5.7 million and a benefit related to the variable accounting of stock options of $544,000 in 2005. Excluding these two non-cash items related to stock options, our operating expenses were $10.8 million, or 11%, lower in 2006 than in 2005, primarily due to decreases in expenditures in 2006 following our 2005 restructuring.

In order to analyze and compare our results of operations to 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.

Research and Development Expenses

For the year ended December 31, 2006, our total research and development expenses were $80.6 million; compared to $82.5 million for the same period in 2005. The decrease of $1.9 million from 2005 to 2006 was primarily due to cost savings achieved as a result of our focus on key programs. Our total R&D expenses in 2006 included compensation expense associated with stock options of $4.5 million. Excluding this non-cash item, our total R&D expenses decreased by $6.4 million, or 8% in 2006 compared to 2005.

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

	December 31,	
	2006	2005
Research and development expenses	$76,026	$82,467
Non-cash compensation expense related to stock options	4,541	—
Total research and development as reported	$80,567	$82,467

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

	December 31,	
	2006	2005
Drug Discovery and Development	$66,893	$69,536
Ibis Biosciences	13,674	12,931
Total research and development expenses	$80,567	$82,467

Drug Discovery & Development

Antisense Drug Discovery

Using proprietary antisense oligonucleotides to identify what a gene does, called gene functionalization, and then determining whether a specific gene is a good target for drug discovery, called target validation, are the first steps in our drug discovery process. We use our proprietary antisense technology to generate information about the function of genes and to determine the value of genes as drug discovery targets. We use this information to direct our own antisense drug discovery research, and that of our antisense drug discovery partners. Antisense drug discovery is also the function within Isis that is responsible for advancing antisense core technology.

As we have advanced our antisense technology to a point where we and our partners now have extensive clinical and preclinical development pipelines that are full of product opportunities, we have far more drug assets than we can afford to develop on our own. As a result, we have significantly reduced our antisense drug discovery activities so that we can focus on our drugs in development. 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 discovery costs for the year ended December 31, 2006 were $14.5 million, compared to $17.9 million for 2005. The decrease of $3.4 million from 2005 to 2006 was principally the result of cost savings achieved as a result of our increased focus on our key programs. These cost savings were primarily attributed to a decrease in personnel costs. In addition, under our Lilly collaboration extension, we are no longer reimbursing Lilly for the cost of their scientists who are supporting the joint collaboration.

Antisense Drug Development

Our development activities reflect our efforts to advance our drugs through the various stages of preclinical, or animal studies, and human clinical trials. The development plans for our drugs are subject to numerous uncertainties like obtaining regulatory approval, market availability and successfully obtaining funding, which affects our research and development expenditures and capital resources. Prior to starting clinical trials, we test our potential products in numerous preclinical studies to identify disease indications for which they may be candidates. Once we have established that a preclinical drug has met certain clinical requirements and we have filed an Investigational New Drug Application, or IND, with the FDA, we may initiate clinical trials in the United States for that drug. It may take several years to complete clinical trials, with the length varying substantially according to the complexity, novelty and intended use of the product candidate. The following timelines represent our estimate of typical completion times for clinical trials we generally conduct: Phase 1—one year, Phase 2—one to two years, and Phase 3—two to four years. However, a number of factors including the required minimum number of patients, the ability to enroll suitable patients, the dosing regimens and the requisite follow-up periods, the clinical endpoints and input from our corporate partners, tend to vary from product to product and can impact the timing and magnitude of what we spend on each product in a particular period. These factors are outside our control and often result in dramatic fluctuations in the costs associated with each product on a period to period basis. As a result, we are unable to estimate the costs to complete our projects.

We may conduct multiple clinical trials on a drug, 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 drugs in certain indications in order to focus our resources on more promising drugs or indications. For example, in early 2005, we decided not to initiate additional studies of ISIS 14803 and ISIS 104838. Generally, Phase 3 clinical trials are the longest, largest and most expensive component of the drug development process. Further, products in Phase 3 trials represent the most near term possibility of commercial success. In addition, because Phase 3 trials typically involve a well-defined protocol and require dedicated resources, it is easier for us to separately capture costs associated with these projects. 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, eleven of our 17 drugs, which substantially reduces our development costs.

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

	December 31,	
	2006	2005
Alicaforsen for Crohn's disease	$ 5	$ 417
Other antisense development products	21,205	22,430
Development overhead costs	4,183	3,475
Non-cash compensation expense related to stock options	1,468	—
Total antisense drug development	$26,861	$26,322

Antisense drug development expenditures were $25.4 million, excluding $1.5 million of non-cash stock compensation expense, and $26.3 million for the years ended December 31, 2006 and 2005, respectively. The decrease of $929,000 for 2006 compared to 2005 was primarily due to a decrease in costs associated with development activities for our first generation drugs, including alicaforsen for Crohn's disease. In addition, we realized cost savings due to our decision to focus our research and development resources on our most promising second generation drugs, including ISIS 301012 and ISIS 113715, and the resulting decision to discontinue development of ISIS 104838 and ISIS 14803. We expect our drug development expenses to fluctuate based on the timing and size of our clinical trials.

We incurred development expenditures related to alicaforsen for Crohn's disease of $5,000 and $417,000 for the years ended December 31, 2006 and 2005, respectively. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with Crohn's disease. In these trials, alicaforsen did not demonstrate statistically significant induction of clinical remission compared to placebo. As a result of this data, we decided not to invest further in the development of alicaforsen for Crohn's disease. The 2006 and 2005 expenses represent costs associated with closing out the program.

We incurred expenses related to our other products in development of $21.2 million and $22.4 million for the years ended December 31, 2006 and 2005, respectively. The decrease of $1.2 million in 2006 was primarily the result of a decrease in development activity related to alicaforsen for ulcerative colitis and the discontinuation of ISIS 104838 and ISIS 14803. In December 2004, we announced the results of three Phase 2 studies of alicaforsen enema to treat patients with ulcerative colitis in which alicaforsen enema produced significant and long-lasting disease improvement. Costs for alicaforsen for ulcerative colitis have decreased in 2006 as compared to 2005 because we were using primarily internal resources as we prepared Phase 3 development plans for the drug. The decreases were offset in part by increased expenditures related to our most promising second generation drugs, specifically ISIS 113715 for the treatment of diabetes and ISIS 301012 for the lowering of high cholesterol. We are currently conducting multiple Phase 2 trials for ISIS 301012.

Development overhead costs were $4.2 million and $3.5 million for the years ended December 31, 2006 and 2005, respectively. The increase of $708,000 million for 2006 compared to 2005 was primarily due to increased personnel costs and costs associated with our amended license agreement with Ajinomoto.

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. These costs for the years ended December 31, 2006 and 2005 were $6.6 million and $6.5 million, respectively. This function is responsible for providing drug supplies to antisense drug discovery and antisense drug development, including the analytical testing to satisfy good laboratory and good manufacturing practices requirements.

Ibis Biosciences, Inc.

Ibis' research and development expenses are primarily the result of its performance under government contracts in support of the ongoing development of the Ibis T5000 Biosensor System and related assay kits. Ibis' expenses include all contract-related costs it incurs on behalf of government agencies in connection with the performance of its obligations under the respective contracts, including costs for equipment to which the government retains title. Research and development expenditures in Ibis include costs for scientists, pass-through equipment costs, laboratory supplies, chemicals and highly specialized information technology consultants to advance the research and development of the Ibis T5000 Biosensor System. Further, we allocate a portion of R&D support costs and selling, general and administrative costs to Ibis Biosciences.

Ibis' research and development expenses, excluding $746,000 of non-cash compensation expense related to stock options for 2006, were $12.9 million for the years ended December 31, 2006 and 2005. In 2006, Ibis incurred costs to support deployed Ibis biosensor systems and the preparations necessary to move towards commercialization. These costs were offset by a decrease in pass-through equipment costs under our government contracts in 2006 compared to 2005. Ibis has delivered four systems to its government partners for use in biodefense and epidemiological surveillance and one system under a commercial purchase order. The first commercial system, which was delivered in the fourth quarter of 2006, was part of an order for two Ibis T5000 Biosensor Systems from a U.S. government agency for human forensics applications. Ibis expects to deliver the second system under this order in early 2007. We expect costs and expenses for Ibis 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 for the years ended (in thousands):

	December 31, 2006	December 31, 2005
Personnel costs	$ 5,978	$ 5,739
Occupancy	5,868	6,931
Depreciation and amortization	6,955	5,696
Insurance	995	1,123
Other	1,720	2,055
Total R&D support costs	$21,516	$21,544

R&D support costs for the years ended December 31, 2006 and 2005 were both $21.5 million. In 2006, depreciation and amortization costs decreased compared to 2005 as a result of an increase in write-offs of patent application costs compared to 2005, offset in part by a decrease in facilities and equipment depreciation in 2006 compared to 2005. The decrease in facilities and equipment depreciation in 2006 compared to 2005 was the result of the consolidation and closure of facilities in 2005 resulting from our reorganization in 2005. In 2006 and 2005, we allocated $2.5 million and $2.8 million, respectively, of our R&D support costs to Ibis Biosciences.

For the years ended December 31, 2006 and December 31, 2005, our R&D support costs by segment were as follows (in thousands):

	December 31, 2006	December 31, 2005
Drug Discovery and Development	$18,998	$18,771
Ibis Biosciences	2,518	2,773
Total R&D support costs	$21,516	$21,544

Selling, General and Administrative Expenses

Selling, general and administrative expenses include corporate costs required to support our company, our employees and our stockholders. These costs include personnel and outside costs in the areas of business development, legal, human resources, investor relations, finance and Ibis sales and marketing. Additionally, we include in selling, general and administrative expenses such costs as rent, repair and maintenance of buildings and equipment, depreciation, utilities, information technology and procurement costs that we need to support the corporate functions listed above. Beginning in 2006, as a result of the consolidation of Symphony GenIsis, selling, general and administrative expenses also include Symphony GenIsis' general and administrative expenses.

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

	December 31, 2006	December 31, 2005
Selling, general and administrative expenses	$11,413	$8,432
Non-cash compensation expense related to stock options	1,206	—
Total selling, general and administrative as reported	$12,619	$8,432

Selling, general and administrative expenses, excluding non-cash compensation expense related to stock options, for the year ended December 31, 2006 totaled $11.4 million compared to $8.4 million for 2005. The increase for 2006 compared to 2005 was 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, which we settled in August 2006. As Ibis continues to execute its commercialization plan, we expect selling, general and administrative expenses for Ibis to continue to increase.

For the years ended December 31, 2006 and December 31, 2005, our selling, general and administrative expenses by segment were as follows (in thousands):

	December 31, 2006	December 31, 2005
Drug Discovery and Development	$ 9,680	$7,342
Ibis Biosciences	2,939	1,090
Total selling, general and administrative expenses	$12,619	$8,432

Compensation Benefit Related to the Variable Accounting of Stock Options

Compensation benefit related to the variable accounting of stock options for the year ended December 31, 2005 was $544,000. Prior to the adoption of SFAS 123R, on January 1, 2006, we accounted for options affected by the employee stock option exchange program initiated in April 2003 as variable stock options in accordance with APB 25 and FIN 44.

Restructuring Activities

During the year ended December 31, 2006, we recorded a benefit of $536,000 compared to $7.0 million of expense in 2005 for restructuring activities resulting from our decision to focus our resources on key programs.

In 2006, we successfully negotiated a contract modification settlement with one of our vendors. The amount of the contract termination cost was $265,000 less than the amount we had previously accrued. Additionally, 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 we had previously accrued. These benefits were included in the restructuring activities for the year ended December 31, 2006.

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.

Investment Income

Investment income for the years ended December 31, 2006 and 2005 was $6.0 million and $5.1 million, respectively. The increase in interest income in 2006 over 2005 was primarily due to our higher average returns on our investments resulting from higher interest rates for 2006 compared to 2005 and a higher average cash balance as a result of the funds held by Symphony GenIsis and the proceeds received from the Azimuth equity financing. As a result of the additional cash held by Symphony GenIsis, the cash received from Azimuth, and the net proceeds from the issuance in January 2007 of the $162.5 million of 2⅝% convertible subordinated notes due 2027, we expect investment income to increase in 2007.

Interest Expense

Interest expense for the year ended December 31, 2006 was $9.0 million, compared to $20.3 million for the same period in 2005. The $11.3 million decrease from 2005 to 2006 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. The reduced interest rate of the 2⅝% notes compared to the 5½% notes reduces our annual cash interest payment by approximately $2.6 million.

Gain on Investments, net

Gain on investments for 2006 was $2.3 million and $0 for 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 reflected the decrease in the market value of ATL's stock, which we believe was a result of the financial market conditions related to biotechnology companies at that time.

Net Loss Applicable to Common Stock

For the years ended December 31, 2006 and 2005, net loss applicable to common stock was $45.9 million and $72.4 million, respectively. We recognized a benefit of $23.0 million for 2006 in the Loss Attributable to Noncontrolling Interest in Symphony GenIsis, Inc., resulting from our collaboration with Symphony GenIsis. This benefit was a significant reason for the improvement in our net loss applicable to common stock in 2006 compared to 2005. The decrease in the net loss applicable to common stock was also impacted by a net gain on investments and a decrease in interest expense, offset in part by an increase in our loss from operations.

Net Loss per Share

Net loss per share for 2006 was $0.62 per share compared to $1.15 per share in 2005. During 2005, we issued 12 million shares of common stock in a private placement that raised net proceeds of approximately $48 million and 2.5 million shares to Lilly in connection with the conversion of our $100 million Lilly loan. Additionally, in 2006, we issued approximately 8.0 million shares of common stock to Azimuth under an equity financing that raised proceeds of $75 million and we issued approximately 2.0 million shares in connection with the exercise of stock options and warrants. These additional shares, combined with the substantial decrease in net loss applicable to common stock, explain the significant decrease in our net loss per share for 2006 compared to 2005.

Net Operating Loss Carryforward

At December 31, 2006, we had federal, foreign and California tax net operating loss carryforwards of approximately $560.0 million, $1.0 million, and $179.5 million, respectively. We also had federal and California research credit carryforwards of approximately $25.7 million and $18.5 million, respectively. The net operating losses, research credit carryforwards, and capitalized research expense make up the majority of our deferred tax assets. Subject to the limitation described below, we will use the net operating loss and research credits, and realize the benefit of these deferred tax assets if we become profitable. We fully reserved all of our deferred tax assets, as their realization is uncertain. Our federal tax loss carryforwards will begin expiring in 2007, unless previously utilized. Our foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership. Our California tax loss carryforwards and our research credit carryforwards began expiring in 2005 and 2006, respectively, unless utilized. Our net operating loss and tax credit carryforwards will be subject to an annual limitation regarding utilization against taxable income in future periods due to "change of ownership" provisions of the Tax Reform Act of 1986. We believe that such limitation will not have a material adverse impact on the benefits that may arise from our net operating loss and tax credit carryforwards. However, there may be additional limitations arising from any future changes in ownership that may have a material adverse impact on us.

Years Ended December 31, 2005 and December 31, 2004

Revenue

Total revenue for the year ended December 31, 2005 was $40.1 million, compared to $42.6 million for the same period in 2004. Significant components of 2005 revenue included $7.0 million from Drug Royalty USA, Inc., as a partial payment for the acquisition of a part of our royalty rights in Macugen; approximately $3.7 million from Alnylam associated with the inclusion of our technology in its collaboration with Novartis; $2.7 million from OncoGenex for the expansion of the companies' cancer collaboration and the purchase of drug manufactured by us and $2.2 million from our ophthalmology collaboration with Pfizer. Revenue from collaborations was less in 2005 than in 2004 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.

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

	Year Ended December 31,	
	2005	2004
Drug Discovery and Development:		
Research and development revenue	$16,817	$21,684
Licensing and royalty revenue	11,523	10,007
	$28,340	$31,691
Ibis Biosciences:		
Research and development revenue	$11,793	$10,933
Licensing and royalty revenue	—	—
	$11,793	$10,933
Total revenue:		
Research and development revenue	$28,610	$32,617
Licensing and royalty revenue	11,523	10,007
	$40,133	$42,624

Drug Discovery & Development

Research and Development Revenue Under Collaborative Agreements

Our revenue under the category of research and development revenue under collaborative agreements for the year ended December 31, 2005 was $16.8 million, compared to $21.7 million for the same period in 2004. Significant components of our 2005 research and development revenue included $2.2 million from our ophthalmology collaboration with Pfizer and $2.7 million from OncoGenex for the expansion of our cancer collaboration and the purchase of drug manufactured by us. The decrease of $4.9 million was primarily due to a decrease in revenue associated with our collaboration with Lilly.

Licensing and Royalty Revenue

Our revenue from licensing activities and royalties was $11.5 million for the year ended December 31, 2005, compared to $10.0 million for the same period in 2004. The increase of $1.5 million in 2006 was primarily due to $7.0 million in payments from DRC, as a partial payment for part of our royalty rights in Macugen, and approximately $3.7 million from Alnylam associated with the inclusion of our technology in its collaboration with Novartis, offset in part by $4.0 million of milestone payments related to Macugen that we earned from Eyetech and $5.5 million that we earned from Alnylam in 2004.

Ibis Biosciences, Inc.

Research and Development Revenue Under Collaborative Agreements

Ibis generated revenue of $11.8 million for the year ended December 31, 2005, compared to revenue of $10.9 million for the same period in 2004. This increase from 2004 to 2005 was primarily a result of increased funding for internal labor under new and existing government contracts and reflects increased funding to pay for our applications development and technology advancement in support of our commercialization plans for the Ibis biosensor system. The increase from 2004 to 2005 was offset in part by a decrease in revenue earned from pass through equipment purchases. During 2004, Ibis acquired equipment at a cost of $3.2 million to build multiple Ibis biosensor systems. Because Ibis was assembling the systems in 2005 for which it had purchased equipment in 2004, Ibis' equipment purchases during 2005 of $1.2 million were significantly lower than 2004 resulting in reduced revenue and associated expense in 2005 compared to 2004.

Operating Expenses

Total operating expenses were $97.3 million and $160.5 million for the years ended December 31, 2005 and 2004, respectively. We achieved a 39% decrease in our operating expenses in 2005 compared to 2004 principally through a reorganization in early 2005 that focused our resources on key programs. The cost savings we achieved through the reorganization led to a decrease in R&D and G&A expenses of $37.2 million in 2005. A decrease in primarily non-cash costs associated with restructuring activities, consisting principally of inventories, of $25.5 million from 2004 to 2005 also contributed to the reduction in operating expenses.

Total operating expenses for the years ended December 31, 2005 and 2004 included a non-cash compensation benefit of approximately $544,000 and $6,000, respectively, due to variable accounting for stock options.

Research and Development Expenses

For the year ended December 31, 2005, our total research and development expenses were $82.5 million, compared to $118.5 million for the same period in 2004. The substantial decrease of $36.0 million from 2004 to 2005 was primarily due to cost savings achieved as a result of our restructuring activities. These cost savings included significant reductions in personnel, lab supplies and facilities costs as well as reductions in third party clinical development costs attributed to our decision to focus our research and development resources on our most promising second generation drugs and the resulting decision to discontinue development of ISIS 104838, ISIS 14803 and alicaforsen for Crohn's disease.

For the years ended December 31, 2005 and 2004, our research and development expenses by segment were as follows (in thousands):

	December 31,	
	2005	2004
Drug Discovery and Development	$69,536	$105,168
Ibis Biosciences	12,931	13,306
Total research and development expenses	$82,467	$118,474

Drug Discovery & Development

Antisense Drug Discovery

Antisense drug discovery costs for the year ended December 31, 2005 were $17.9 million, compared to $38.4 million for the same period in 2004. The decrease of $20.5 million from 2004 to 2005 was principally the result of cost savings achieved as a result of our restructuring activities. These cost savings were primarily attributed to a decrease in personnel costs. In addition, under our Lilly collaboration extension, we are no longer reimbursing Lilly for the cost of their scientists who are supporting the joint collaboration.

Antisense Drug Development

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

	December 31,	
	2005	2004
Alicaforsen for Crohn's disease	$ 417	$ 5,523
Other antisense development products	22,430	30,202
Development overhead costs	3,475	6,704
Total antisense drug development	$26,322	$42,429

Total antisense drug development expenditures were $26.3 million and $42.4 million for the years ended December 31, 2005 and 2004, respectively. The significant decrease of $16.1 million from 2004 to 2005 was primarily due to a decrease in costs associated with development activities for our first generation drugs, including alicaforsen for Crohn's disease and ulcerative colitis. In addition, we realized cost savings due to our decision to focus our research and development resources on our most promising second generation drugs, including ISIS 301012 and ISIS 113715, and the resulting decision to discontinue development of ISIS 104838 and ISIS 14803.

We incurred development expenditures related to alicaforsen for Crohn's disease of $417,000 and $5.5 million for the years ended December 31, 2005 and 2004, respectively. The decrease of $5.1 million was primarily due to the completion of our Phase 3 trials in December 2004. In December 2004, we reported the results of our Phase 3 clinical trials of alicaforsen in patients with Crohn's disease. In these trials, alicaforsen did not demonstrate statistically significant induction of clinical remission compared to placebo. As a result of these data, we decided not to invest further in the development of alicaforsen for Crohn's disease. The 2005 expenses represent costs associated with closing out the program.

We incurred expenses related to our other products in development of $22.4 million and $30.2 million for the years ended December 31, 2005 and 2004, respectively. The decrease of $7.8 million was primarily the result of a decrease in development activity related to alicaforsen for ulcerative colitis and the discontinuation of ISIS 104838 and ISIS 14803. In December 2004, we announced the results of three Phase 2 studies of alicaforsen enema to treat patients with ulcerative colitis in which alicaforsen enema produced significant and long-lasting disease improvement. Costs for alicaforsen for ulcerative colitis have decreased in 2005 as compared to 2004 because we are using primarily internal resources as we prepare Phase 3 development plans for the drug. The decrease was offset in part by increased expenditures related to our most promising second generation drugs, specifically ISIS 113715 for the treatment of diabetes and ISIS 301012 for the lowering of high cholesterol.

Manufacturing and Operations

Expenditures in our manufacturing and operations function for the year ended December 31, 2005 were $6.5 million. Manufacturing and operations was a new function that was created in 2005 to provide manufacturing efficiencies and related cost savings. We believe that it would be impractical to obtain comparative information for prior periods for this new function, and that such comparisons between any period in 2004 would be meaningless; therefore, we do not discuss these comparisons.

Ibis Biosciences, Inc.

Our Ibis division's research and development expenses for the years ended December 31, 2005 and 2004 were $12.9 million and $13.3 million, respectively. During 2004, Ibis purchased equipment at a cost of $3.2 million to build multiple TIGER biosensor systems. Because Ibis was assembling the systems in 2005 for which it had purchased equipment in 2004, Ibis' equipment purchases during 2005 of $1.2 million were significantly lower than in 2004. The decrease in equipment costs from 2004 to 2005, offset in part by increased costs for personnel and consultants to support the move toward commercialization, were the primary reasons for the decrease in Ibis' research and development expenses from 2004 to 2005.

R&D Support

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

	December 31,	
	2005	2004
Personnel costs	$ 5,739	$10,450
Occupancy	6,931	6,409
Depreciation and amortization	5,696	6,946
Insurance	1,123	1,179
Other	2,055	2,694
Total R&D support costs	$21,544	$27,678

R&D support costs for the years ended December 31, 2005 and 2004 were $21.5 million and $27.7 million, respectively. The decrease in 2005 was primarily due to decreased personnel, facilities, equipment depreciation and patent amortization costs resulting from our restructuring activities, which included employee terminations, consolidation and closure of facilities, and the write-down of equipment and patents. In 2005 and 2004, we allocated $2.8 million and $3.3 million of our R&D support costs to our Ibis division.

For the years ended December 31, 2005 and December 31, 2004, our R&D support costs by segment were as follows (in thousands):

	December 31,	
	2005	2004
Drug Discovery and Development	$18,771	$24,374
Ibis Biosciences	2,773	3,304
Total R&D support costs	$21,544	$27,678

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2005 totaled $8.4 million compared to $9.6 million for 2004. The decrease of $1.2 million from 2004 to 2005 was primarily related to a reduction in personnel and outside services costs resulting from our restructuring activities. We allocated $1.1 million and $924,000 of our general and administrative costs to Ibis in 2005 and 2004, respectively.

For the years ended December 31, 2005 and December 31, 2004, our general and administrative expenses by segment were as follows (in thousands):

	December 31,	
	2005	2004
Drug Discovery and Development	$7,342	$8,658
Ibis Biosciences	1,090	924
Total general and administrative expenses	$8,432	$9,582

Compensation Related to Stock Options

Compensation benefit for the year ended December 31, 2005 was $544,000, compared to compensation benefit of $6,000 for the year ended December 31, 2004. The changes in compensation benefit were primarily related to the effects of using variable accounting to account for stock options associated with the employee stock option exchange program initiated in April 2003. We accounted for options affected by the employee stock option exchange program as variable stock options in accordance with Accounting Principles Board, or APB, Opinion No. 25 and Financial Accounting Standards Board Interpretation, or FIN, No. 44. APB 25 and FIN 44 require us to account for these exchanged options as variable stock options. We also recorded nominal expense in 2005 and 2004 related to stock options granted in prior years to consultants, and we accounted for these options in accordance with Emerging Issues Task Force Abstract No. 96-18, or EITF 96-18.

Restructuring Activities

During the fourth quarter of 2004, we recorded a $32.4 million charge for restructuring activities resulting from our strategic decision to reorganize and focus our resources on key programs. The 2004 charge for restructuring activities consisted of non-cash write-downs of tangible and intangible assets that we considered to be non-essential to our new focus, including excess or idle equipment, inventories, patent costs, and certain prepaid expenses. For the year ended December 31, 2005, we recorded $7.0 million in costs associated with our restructuring activities. 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 connection with the consolidation of our U.S. facilities, we sold three of our buildings during 2005. After deducting commissions, other expenses and the repayment of approximately $5.8 million of debt, we received net proceeds of approximately $7.9 million for the sales of the properties. We included a net gain of $1.5 million on the sales of these buildings in restructuring activities in 2005.

Investment Income

Investment income for the years ended December 31, 2005 and 2004 was $5.1 million and $3.0 million, respectively. The increase in interest income in 2005 over 2004 was primarily due to a gain of $951,000 realized on the sale of a portion of the equity securities of Alnylam that we owned and $2.0 million of non-cash income recorded in connection with the revaluation of warrants issued in connection with our August 2005 private placement. Prior to the registration statement for this private placement becoming effective, the potential existed for us to pay liquidated damages if such effectiveness did not occur. As a result, we allocated a portion of the offering proceeds to the warrants based on the warrants' fair value. We periodically revalued the warrants as a derivative instrument with the change in value recorded as interest income. In the fourth quarter of 2005, the registration statement became effective. As a result, the potential for liquidated damages lapsed resulting in interest income when the warrants were revalued. These increases were offset in part by lower average cash and investments balances in 2005 than in 2004.

Interest Expense

Interest expense for the year ended December 31, 2005 was $20.3 million, compared to $22.6 million for the same period in 2004. The $2.3 million decrease from 2004 to 2005 was primarily due to the effect of a lower debt balance during 2005 than during 2004 resulting from the conversion of our $100 million Lilly loan and a decrease from 2004 to 2005 in the carrying value of our term loan from Silicon Valley Bank. The effect of a lower debt balance in 2005 compared to 2004 was offset in part by the effect of a higher average interest rate in 2005 than in 2004 on our Silicon Valley Bank loan. The Silicon Valley Bank loan 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 7.0% at December 31, 2005, compared to 5.25% at December 31, 2004. The loan is convertible to a fixed interest rate at our option at any time at the then-applicable prime rate plus 1.25%. In 2005, $10.8 million, compared to $13.0 million in 2004, of interest expense did not require cash payment. The amounts represent the accrual of interest expense related to our $100.0 million Lilly loan.

Net Loss Applicable to Common Stock

For the years ended December 31, 2005 and 2004, we reported a net loss of $72.4 million and $142.5 million, respectively. Our net loss applicable to common stock was $72.4 million for the year ended December 31, 2005 and $142.9 million for 2004, including $361,000 of accreted dividends on preferred stock in 2004. There were no accreted dividends on preferred stock in 2005. The decrease in accreted dividends in 2005 from 2004 was the result of our agreement in June 2004 with a subsidiary of Elan to acquire Elan's minority interest in Orasense and HepaSense. In connection with this agreement, Elan transferred its shares of Isis Series B preferred stock to a third party. Immediately upon transfer, these shares converted into 1,055,502 shares of Isis common stock, eliminating the 5% in-kind dividend. The decrease in the net loss applicable to common stock in 2005 from 2004 was primarily the result of a substantial decrease in operating expenses offset by a decrease in revenue, an increase in interest income, and a decrease in interest expense as described previously. In addition, during 2005 and 2004, we incurred charges of $7.0 million and $32.4 million, respectively, related to restructuring activities. In 2005, we did not incur losses on investments. In 2004, we incurred a non-cash loss of $5.1 million principally related to the impairment of our equity investment in Alnylam.

Net Operating Loss Carryforward

At December 31, 2005, we had federal, foreign and California tax net operating loss carryforwards of approximately $510.5 million, $1.0 million, and $120.0 million, respectively. We also had federal and California research credit carryforwards of approximately $25.0 million and $17.5 million, respectively. The net operating losses, research credit carryforwards, and capitalized research expense make up the majority of our deferred tax assets.

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 December 31, 2006, we have earned approximately $507.7 million in revenue from contract research and development and the sale and licensing of our intellectual property. From the time we were founded through December 31, 2006, we have raised net proceeds of approximately $728.8 million from the sale of our equity securities and we have borrowed approximately $386.7 million under long-term debt arrangements to finance a portion of our operations. This amount does not include the $162.5 million of 2⅝% convertible subordinated notes we

issued in January 2007, a portion of which will be used to repurchase our existing 5½% convertible subordinated notes.

At December 31, 2006, we had cash, cash equivalents and short-term investments of $193.3 million, working capital of $181.1 million and stockholders' equity of $68.6 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 reflects the cash received from the Azimuth transaction and the consolidation of the cash and cash equivalents held by Symphony GenIsis. Also contributing to the increase was $10.9 million that we received from stock option exercises in 2006, $4.4 million that we received from the sale of a portion of our Alnylam equity securities in 2006, along with amounts received from contracts, offset by cash used in operations.

As of December 31, 2006, our debt and other obligations totaled $140.3 million, compared to $147.8 million at December 31, 2005. The decrease in our debt and other obligations was primarily due to the declining balance on our Silicon Valley Bank term loan and to a lesser extent the declining balance of our capital lease obligations. We will continue to use lease financing as long as the terms remain commercially attractive.

Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to meet our anticipated requirements through at least the middle of 2010.

The following table summarizes our contractual obligations as of December 31, 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**
5½% Convertible Subordinated Notes	$125.0	$ —	$125.0	$ —	$ —
Standard Operating Debt.....	$ 14.0	$6.7	$ 7.3	$ —	$ —
Capital Lease and Other Obligations.....	$ 1.3	$0.8	$ 0.2	$ —	$ 0.3
Operating Leases.....	$ 22.7	$2.9	$ 5.5	$4.2	$10.1

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 $32.0 million term loan from Silicon Valley Bank to retire debt from two partners. We amortize the term loan over sixty months. The term loan requires 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 8.0% at December 31, 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 December 31, 2006 and 2005 was $14.0 million and $20.2 million, respectively.

In May 2002, we completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. The subordinated notes bear interest at 5½%, which is payable semi-annually, and mature in May 2009. Holders of the subordinated notes can, at any time, convert the notes into shares of common stock at a conversion price of $16.625 per share. At December 31, 2006 and 2005, the principal outstanding on the notes was $125.0 million.

In January 2007, we completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157 million, net of $5.5 million in issuance costs. The $162.5 million convertible subordinated notes bear interest at 2⅛%, which is payable semi-annually, and mature in 2027. These notes are convertible, at the option of the note holders, into approximately 11.1 million shares of common stock at a conversion price of $14.63 per share. We will be able to redeem these notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the 2⅛% notes are also able to require us to repurchase the 2⅛% notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the 2⅛% notes being repurchased plus accrued interest and unpaid interest. Through privately negotiated transactions, we have repurchased approximately $44.1 million aggregate principal amount of the total outstanding of our existing 5½% convertible subordinated notes, and we intend to use a portion of the remaining net proceeds of this offering to repurchase the remaining 5½% notes.

In addition to contractual obligations, we had outstanding purchase orders as of December 31, 2006 for the purchase of services, capital equipment and materials as part of our normal course of business.

We plan to continue to enter into more collaborations with partners to provide for additional revenue 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.

Item 7A. 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 8. Financial Statements and Supplementary Data

We filed our consolidated financial statements and supplementary data required by this item as exhibits hereto, and listed them under Item 15(a)(1) and (2), and incorporated them herein by reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

There have been no reported disagreements on any matter of accounting principles or procedures or financial statement disclosure in 2006 with our Independent Auditors.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Based on our evaluation as of the end of the period covered by this report on Form 10-K, our principal executive officer and principal financial officer have concluded that 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 (the "Exchange Act")) were effective as of December 31, 2006 to ensure that information required to be disclosed by us in reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in SEC rules and forms.

Changes in Internal Controls

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.

Management's Report on Internal Control over Financial Reporting

The management of Isis Pharmaceuticals, Inc. is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Exchange Act Rules 13a-15(f). Isis' internal control over financial reporting is a process designed under the supervision of Isis' Chief Executive Officer and Chief Financial Officer to provide reasonable assurance regarding the reliability of financial reporting and the preparation of Isis' financial statements for external purposes in accordance with United States generally accepted accounting principles.

As of December 31, 2006, management, with the participation of the Chief Executive Officer and Chief Financial Officer, assessed the effectiveness of Isis' internal control over financial reporting based on the criteria for effective internal control over financial reporting established in "Internal Control—Integrated Framework," issued by the Committee of Sponsoring Organizations (COSO) of the Treadway Commission. Based on the assessment, management determined that Isis maintained effective internal control over financial reporting as of December 31, 2006.

Our management's assessment of the effectiveness of our internal control over financial reporting as of December 31, 2006 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their attestation report, which is included elsewhere herein.

Report of Independent Registered Public Accounting Firm on Internal Control Over Financial Reporting

The Board of Directors and Stockholders
Isis Pharmaceuticals, Inc.

We have audited management's assessment, included in the accompanying "Management's Report on Internal Control Over Financial Reporting," that Isis Pharmaceuticals, Inc. maintained effective internal control over financial reporting as of December 31, 2006, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (the COSO criteria). Isis Pharmaceuticals' management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting. Our responsibility is to express an opinion on management's assessment and an opinion on the effectiveness of the company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, evaluating management's assessment, testing and evaluating the design and operating effectiveness of internal control, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed 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. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion, management's assessment that Isis Pharmaceuticals, Inc. maintained effective internal control over financial reporting as of December 31, 2006, is fairly stated, in all material respects, based on the COSO criteria. Also, in our opinion, Isis Pharmaceuticals, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2006, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets as of December 31, 2006 and 2005, and the related consolidated statements of operations, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2006 of Isis Pharmaceuticals, Inc. and our report dated March 6, 2007 expressed an unqualified opinion thereon.

/s/ ERNST & YOUNG LLP

San Diego, California
March 6, 2007

Item 9B. Other Information

Atlantic Healthcare (UK) Limited

In March 2007, we licensed alicaforsen to Atlantic Healthcare (UK) Limited, a UK-based company that was founded in 2006 by gastrointestinal drug developers to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Healthcare plans to initially develop alicaforsen for pouchitis, an ulcerative colitis indication, followed by ulcerative colitis and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, we will receive an upfront payment from Atlantic Healthcare in the form of equity valued at $2 million. In addition, assuming Atlantic Healthcare successfully develops and commercializes alicaforsen, we will receive milestone payments and royalties on future product sales of alicaforsen. If Atlantic Healthcare meets certain of these milestones, at Atlantic Healthcare's request, we will attempt to identify a second generation lead drug candidate for Atlantic Healthcare. Atlantic Healthcare may take an exclusive worldwide license to the lead candidate under the terms and conditions of the agreement. Atlantic Healthcare is solely responsible for the continued development of alicaforsen, and, if selected, the second generation lead drug candidate.

PART III

Item 10. Directors and Executive Officers of the Registrant

We incorporate by reference the information required by this Item with respect to Directors and the Audit Committee by reference from the information under the caption "Election of Directors," "Nominating, Governance and Review Committee" and "Audit Committee," respectively, contained in our definitive Proxy Statement (the "Proxy Statement"), which we will file on or about April 5, 2007 with the Securities and Exchange Commission in connection with the solicitation of proxies for our 2007 Annual Meeting of Stockholders to be held on May 17, 2007.

We incorporate by reference the required information concerning our Code of Ethics from the information under the caption "Code of Ethics" contained in the Proxy Statement. We have filed our Code of Ethics as an exhibit to this Report on Form 10-K.

Item 1, Part I of this Report contains the required information concerning our Executive Officers. We incorporate by reference the information required by this Item concerning compliance with Section 16(a) of the Securities Exchange Act of 1934, as amended, from the information under the caption "Section 16(a) Beneficial Ownership Reporting Compliance" contained in the Proxy Statement.

Item 11. Executive Compensation

We incorporate by reference the information required by this item to the information under the caption "Executive Compensation", "Compensation Committee Interlocks and Insider Participation" and "Compensation Committee Report" contained in the Proxy Statement.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

We incorporate by reference the information required by this item to the information under the captions "Security Ownership of Certain Beneficial Owners and Management" contained in the Proxy Statement.

Securities Authorized for Issuance Under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2006.

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders(a)	5,554,000	$7.17	2,970,000 (c)
Equity compensation plans not approved by stockholders(b)	2,102,000	$8.62	2,201,000
Total	7,656,000	$7.57	5,171,000

(a) Consists of three Isis plans: 1989 Stock Option Plan, 2002 Non-Employee Directors' Stock Option Plan and ESPP.

(b) Consists of the 2000 Broad-Based Equity Incentive Plan, more fully described below.

(c) Of these shares, 100,054 remained available for purchase under the ESPP as of December 31, 2006. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year through and including 2009, we automatically increase the aggregate number of shares reserved for issuance under the plan by 200,000 shares.

Description of 2000 Broad-Based Equity Incentive Plan

We adopted the 2000 Broad-Based Equity Incentive Plan, or the 2000 Plan, to provide our employees, officers, directors and consultants an opportunity to benefit from increases in the value of our common stock through the granting of non statutory stock options, stock bonuses and rights to purchase restricted stock. At the time we adopted the 2000 Plan, we were not required to seek the approval of our stockholders. The Board has delegated administration of the 2000 Plan to the Compensation Committee of the Board, and the Compensation Committee has delegated administration of the 2000 Plan to the Non-Management Stock Option Committee with respect to certain option grants to employees who are not our executive officers. The Board has the power to construe and interpret the 2000 Plan and, subject to the provisions of the 2000 Plan, to select the persons to whom stock awards are to be made, to designate the number of shares to be covered by each stock award, to establish vesting schedules, to specify the exercise price and the type of consideration to be paid to us upon exercise or purchase.

As of December 31, 2006, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 2,102,000 shares have been granted and were outstanding under the 2000 Plan, options to purchase an aggregate of 1,686,000 shares have been exercised under the 2000 Plan, and 2,201,000 shares remained available for grant thereunder.

Options granted under the 2000 Plan generally have a term of ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25% per year after the first year and then at the rate of 2.08% per month thereafter during the option holder's employment or service as a consultant, employee or director. Options granted pursuant to the April 2003 stock option exchange program as discussed in Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations," and in the Notes to Consolidated Financial Statements, 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 or service as a consultant, employee or director. If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization,

reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the 2000 Plan appropriately in the class(es) and maximum number of securities subject to the 2000 Plan, and we will adjust the outstanding stock awards appropriately in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our Board will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

In the event of our dissolution or liquidation, all outstanding stock awards will terminate immediately prior to such event.

In the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise;

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, we will accelerate the vesting of such stock awards in full (and, if applicable, the time during which such stock awards may be exercised) and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event. As of December 31, 2006, approximately 97,661 stock awards granted under the 2000 plan will be accelerated in full if a transaction described above occurs, even if the surviving corporation assumes such award.

Item 13. Certain Relationships and Related Transactions

We incorporate by reference the information required by this item to the information under the caption "Certain Relationships and Related Transactions" contained in the Proxy Statement.

Item 14. Principal Accountant Fees and Services

We incorporate by reference the information required by this item to the information under the caption "Ratification of Selection of Independent Auditors" contained in the Proxy Statement.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a)(1) Index to Financial Statements

We submitted the consolidated financial statements required by this item in a separate section beginning on page F-1 of this Report.

(a)(2) Index to Financial Statement Schedules

We omitted these schedules because they are not required, or are not applicable, or the required information is shown in the consolidated financial statements or notes thereto.

(a)(3) Index to Exhibits

See Index to Exhibits beginning on page 83.

(b) Exhibits

We listed the exhibits required by this Item under Item 15(a)(3).

(c) Financial Statement Schedules

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Registrant has duly caused this report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized on the 14th day of March, 2007.

ISIS PHARMACEUTICALS, INC.

By: /S/ STANLEY T. CROOKE
Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board, President and Chief Executive Officer (Principal executive officer)

POWER OF ATTORNEY

KNOW ALL MEN BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Stanley T. Crooke and B. Lynne Parshall, or any of them, his or her attorney-in-fact, each with the power of substitution, for him or her in any and all capacities, to sign any amendments to this Report, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, hereby ratifying and confirming all that each of said attorneys-in-fact, or his or her substitute or substitutes, may do or cause to be done by virtue hereof.

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)	March 14, 2007
/S/ B. LYNNE PARSHALL B. Lynne Parshall, J.D.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	March 14, 2007
/S/ SPENCER R. BERTHELSEN Spencer R. Berthelsen, M.D.	Director	March 14, 2007
/S/ RICHARD D. DIMARCHI Richard D. DiMarchi	Director	March 14, 2007
/S/ JOSEPH KLEIN Joseph Klein, III.	Director	March 14, 2007
/S/ FREDERICK T. MUTO Frederick T. Muto	Director	March 14, 2007
/S/ JOHN C. REED, M.D. PH.D. John C. Reed, M.D., Ph.D.	Director	March 14, 2007
/S/ JOSEPH H. WENDER Joseph H. Wender	Director	March 14, 2007

INDEX TO EXHIBITS

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation filed June 19, 1991.(1)
3.2	Certificate of Amendment to Restated Certificate of Incorporation filed May 3, 2006.(3)
3.3	Bylaws.(19)
4.3	Certificate of Designation of the Series C Junior Participating Preferred Stock.(17)
4.4	Specimen Common Stock Certificate.(1)
4.5	Form of Right Certificate.(17)
4.6	Subscription, Joint Development and Operating Agreement dated January 14, 2000 among the Registrant, Elan Corporation, plc, Elan International Services, Ltd. and Hepasense, Ltd. (with certain confidential information deleted), together with the related Securities Purchase Agreement, Convertible Promissory Note, Warrant to Purchase Shares of Common Stock, Registration Rights Agreement and License Agreements.(14)
4.7	Registration Rights Agreement, dated May 1, 2002, among the Registrant, UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc., and Roth Capital Partners, LLC.(16)
4.8	Indenture, dated as of May 1, 2002, between the Registrant and Wells Fargo Bank Minnesota, National Association, as Trustee, with respect to the $125,000,000 5½% Convertible Subordinated Notes due 2009.(16)
4.9	Form of 5½% Convertible Subordinated Note due 2009.(16)
4.10	Securities Purchase Agreement, dated August 19, 2005, by and among the Registrant and the purchasers listed on Exhibit A thereto.(37)
4.11	Form of Warrant dated August 23, 2005.(37)
4.12	Indenture, dated January 23, 2007, between the Registrant and Wells Fargo Bank, N.A., a national banking association, as trustee, including Form of 2⅝% Convertible Subordinated Note due 2027.(42)
4.13	Registration Rights Agreement, dated January 23, 2007, among the Registrant and the Initial Purchasers identified therein.(42)
4.14	Registration Rights Agreement between the Registrant and Symphony GenIsis Holdings LLC dated April 7, 2006 (with certain confidential information deleted).(3)
4.15	Form of Warrant dated April 7, 2006 issued to Symphony GenIsis Holdings LLC.(3)
10.1	Form of Indemnification Agreement entered into between the Registrant and its Directors and Officers with related schedule.(1)
10.2*	Registrant's 1989 Stock Option Plan, as amended.(2)
10.4*	Registrant's Employee Stock Purchase Plan.(10)
10.5	Form of Employee Assignment of Patent Rights.(1)
10.6*	Registrant's 2000 Broad-Based Equity Incentive Stock Option Plan and related form of option agreement.(10)

Exhibit Number	Description of Document
10.11	Asset Purchase Agreement between the Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).(6)
10.13	Patent Rights Purchase Agreement between the Registrant and Gilead Sciences, Inc., dated December 18, 1998 (with certain confidential information deleted).(9)
10.14	Rights Agreement dated as of December 8, 2000 between the Registrant and American Stock Transfer & Trust Company.(17)
10.15	Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted).(19)
10.17	Subcontract Agreement, dated October 25, 2001 between the Registrant and Science Applications International Corporation.(21)
10.18	Master Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.19	Collaboration and License Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.20	Clinical Supply Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited (with certain confidential information deleted).(24)
10.21	Stock Purchase Agreement dated October 30, 2001 between the Registrant and Antisense Therapeutics Limited.(24)
10.22	Collaboration and Co-development Agreement, dated November 16, 2001 between the Registrant and OncoGenex Technologies Inc. (with certain confidential information deleted).(22)
10.23	Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.24	Amended and Restated IDT-Isis Licensing Agreement dated December 4, 2001 between the Registrant and Integrated DNA Technologies, Inc. (with certain confidential information deleted).(24)
10.26	License Agreement dated December 31, 2001 between the Registrant and Eyetech Pharmaceuticals, Inc. (with certain confidential information deleted).(25)
10.35	Registrant's Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 30, 2005.(38)
10.36*	Registrant's Amended and Restated 2002 Non-Employee Directors' Stock Option Plan.(43)
10.37*	Registrant's Form of 2002 Non-Employee Directors' Stock Option Agreement.(31)
10.41*	Form of Severance Agreement dated April 2003 entered into between the Registrant Stanley T. Crooke and B. Lynne Parshall.(32)
10.42	Grant letter dated September 29, 2003 from the Centers for Disease Control and Prevention (with certain confidential information deleted).(33)
10.43*	Amendment No. 1 to Isis Pharmaceuticals, Inc. Employee Stock Purchase Plan.(33)

Exhibit Number	Description of Document
10.44	Loan and Security Agreement dated December 15, 2003 between the Registrant and Silicon Valley Bank, including the related negative pledge agreement.(12)
10.47	Subcontract No. 44076514 dated February 26, 2004 between the Registrant and Science Applications International Corporation (with certain confidential information deleted).(13)
10.48	Strategic Collaboration and License Agreement dated March 11, 2004 between the Registrant and Alnylam Pharmaceuticals, Inc. (with certain confidential information deleted).(18)
10.50	Securities Purchase Agreement dated June 4, 2004 between the Registrant and Elan Pharmaceutical Investments II, Ltd.(26)
10.51	Development Agreement dated September 30, 2004 between the Registrant and the National Institute of Allergy and Infectious Diseases (with certain confidential information deleted).(34)
10.52	Amendment No. 1 to License Agreement between the Registrant and Eyetech.(39)
10.53	Sale and Assignment Agreement between the Registrant and Drug Royalty USA, Inc., dated December 21, 2004 (with certain confidential information deleted).(39)
10.54	Security Agreement between the Registrant and Drug Royalty USA, Inc, dated December 21, 2004 (with certain confidential information deleted).(39)
10.55*	Form of Option Agreement for Options Granted after March 8, 2005 under the 1989 Stock Option Plan.(39)
10.56*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2000 Broad-Based Equity Incentive Plan.(39)
10.57*	Form of Option Agreement for Options Granted after March 8, 2005 under the 2002 Non-Employee Director's Stock Option Plan.(39)
10.58	Collaboration and License Agreement between the Registrant and Sarissa, Inc., dated Feb 10, 2005.(39)
10.59	Amendment No.1 to Rights Agreement dated April 7, 2005.(35)
10.60	Collaborative Research Agreement dated May 24, 2005 between the Registrant and Pfizer Inc (with certain confidential information deleted).(36)
10.61	Lease Agreement dated September 6, 2005 between the Registrant and BMR-2282 Faraday Avenue LLC.(38)
10.62	Second Amended and Restated Collaboration Agreement dated August 5, 2005 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).(38)
10.63	Notice of Grant Award issued August 1, 2005 by the Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Disease (with certain confidential information deleted).(38)
10.64	Form of Subcontract Agreement between the Registrant and Science Applications International Corporation.(38)
10.65*	Letter dated February 27, 2006 extending Dr. Crooke's severance benefit agreement.(40)
10.66*	Letter dated February 27, 2006 extending Ms. Parshall's severance benefit agreement.(40)

Exhibit Number	Description of Document
10.67	Purchase Agreement, dated January 17, 2007, among the Registrant and the Initial Purchasers identified therein.(42)
10.68	Purchase Option Agreement among the Registrant, Symphony GenIsis Holdings LLC and Symphony GenIsis Inc. dated April 7, 2006 (with certain confidential information deleted).(3)
10.69	Novated and Restated Technology License Agreement among the Registrant, Symphony GenIsis Holdings LLC and Symphony GenIsis Inc. dated April 7, 2006 (with certain confidential information deleted).(3)
10.70	Amended and Restated Research and Development Agreement among the Registrant, Symphony GenIsis Holdings LLC and Symphony GenIsis Inc. dated April 7, 2006 (with certain confidential information deleted).(3)
10.71*	Severance Agreement dated February 1, 2007 between the Registrant and Jeffrey M. Jonas.(44)
10.72	Manufacturing, Commercialization and Development Agreement between the Registrant and Bruker Daltonics, Inc. dated July 31, 2006 (with certain confidential information deleted).(45)
10.73*	Retention Agreement dated March 1, 2007 between the Registrant and Mark K. Wedel.(47)
14.1	Registrant's Code of Ethics and Business Conduct.(12)
21.1	List of Subsidiaries for the Registrant.
23.1	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm.
24.1	Power of Attorney.(46)
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.
99.2	Form of Confidentiality Agreement.(11)

(1) Filed as an exhibit to the Registrant's Registration Statement on Form S-1 (No. 33-39640) or amendments thereto and incorporated herein by reference.

(2) Filed as an exhibit to Registrant's Notice of Annual Meeting and Proxy Statement for the 2004 Annual Meeting of Stockholders, filed with the SEC on April 12, 2004, and incorporated herein by reference.

(3) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2006.

(4) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1996 and incorporated herein by reference.

(5) Reserved.

(6) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1997 and incorporated herein by reference.

(7) Reserved.

(8) Reserved.

(9) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1998 and incorporated herein by reference.

(10) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1999 and incorporated herein by reference.

(11) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-71911) or amendments thereto and incorporated herein by reference.

(12) Filed as an exhibit to the Registrant's Annual Report Form 10-K for the year ended Dec 31, 2003 and incorporated herein by reference.

(13) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2004 and incorporated herein by reference.

(14) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 28, 2000, as amended on October 5, 2001, and incorporated herein by reference.

(15) Reserved.

(16) Filed as an exhibit to the Registrant's Registration Statement on Form S-3 (No. 333-89066), originally filed on May 24, 2002, or amendment thereto and incorporated by reference.

(17) Filed as an exhibit to Registrant's Report on Form 8-K dated December 8, 2000 and incorporated herein by reference.

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

(19) Filed as an exhibit to the Registrant's report on Form 10-Q as amended for the quarter ended June 30, 2001 and incorporated herein by reference.

(20) Reserved.

(21) Filed as an exhibit to the Registrant's Report on Form 8-K filed October 29, 2001 and incorporated herein by reference.

(22) Filed as an exhibit to the Registrant's Report on Form 8-K filed December 12, 2001 and incorporated herein by reference.

(23) Reserved.

(24) Filed as an exhibit to the Registrant's Report on Form 8-K filed January 4, 2002 and incorporated herein by reference.

(25) Filed as an exhibit to the Registrant's Report on Form 8-K dated January 7, 2002 and incorporated herein by reference.

(26) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2004 and incorporated herein by reference.

(27) Reserved.

(28) Reserved.

(29) Reserved.

(30) Reserved.

(31) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2001 and incorporated herein by reference.

(32) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended June 30, 2003 and incorporated herein by reference.

(33) Filed as an exhibit to the Registrant's Report on Form 10-Q for the quarter ended September 30, 2003 and incorporated herein by reference.

(34) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2004 and incorporated herein by reference.

(35) Filed as an exhibit to Registrant's Current Report on Form 8-K dated April 7, 2005 and incorporated herein by reference.

(36) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 2005 and incorporated herein by reference.

(37) Filed as an exhibit to Registrant's Current Report on Form 8-K dated August 22, 2005 and incorporated herein by reference.

(38) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2005 and incorporated herein by reference.

(39) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2004 and incorporated herein by reference.

(40) Filed as an exhibit to Registrant's Current Report on Form 8-K dated February 27, 2006 and incorporated herein by reference.

(41) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 2005 and incorporated herein by reference.

(42) Filed as an exhibit to Registrant's Current Report on Form 8-K dated January 24, 2007 and incorporated herein by reference.

(43) Filed as an exhibit to the Registrant's Current Report on Form 8-K, filed with the SEC on May 5, 2006 and incorporated herein by reference.

(44) Filed as an exhibit to Registrant's Current Report on Form 8-K dated February 1, 2007 and incorporated herein by reference.

(45) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 2006 and incorporated herein by reference.

(46) Filed as part of this Annual Report on Form 10-K for the year ended December 31, 2006, reference is made to page 82.

(47) Filed as an exhibit to the Registrants' Current Report on Form 8-K dated March 1, 2007 and incorporated herein by reference.

* Indicates management compensatory plans and arrangements as required to be filed as exhibits to this Report pursuant to Item 14(c).

ISIS PHARMACEUTICALS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders
Isis Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 2006 and 2005, and the related consolidated statements of operations, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2006. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the consolidated financial position of Isis Pharmaceuticals, Inc. at December 31, 2006 and 2005, and the results of its consolidated operations and its cash flows for each of the three years in the period ended December 31, 2006, in conformity with U.S. generally accepted accounting principles.

As discussed in Note 1 to the consolidated financial statements, Isis Pharmaceuticals, Inc. changed its method of accounting for Share-Based Payments in accordance with Statement of Financial Accounting Standards No. 123 (revised 2004) on January 1, 2006.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the effectiveness of Isis Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2006, based on the criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated March 6, 2007, expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

San Diego, California
March 6, 2007

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

	December 31, 2006	December 31, 2005
ASSETS		
Current assets:		
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $54.8 million and $0 at December 31, 2006 and December 31, 2005, respectively)	$ 114,514	$ 50,885
Short-term investments	78,819	43,504
Contracts receivable	2,395	3,918
Inventory	861	951
Other current assets	9,614	6,600
Total current assets	206,203	105,858
Property, plant and equipment, net	7,157	9,130
Licenses, net	21,435	23,770
Patents, net	16,836	18,773
Deposits and other assets	4,276	8,842
Total assets	$ 255,907	$ 166,373
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 4,288	$ 2,095
Accrued compensation	6,222	3,706
Accrued liabilities	6,071	8,643
Current portion of long-term obligations	7,514	7,835
Current portion of deferred contract revenue	1,044	1,514
Total current liabilities	25,139	23,793
5½% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	7,822	14,915
Long-term deferred contract revenue	44	—
Total liabilities	158,005	163,708
Noncontrolling interest in Symphony GenIsis, Inc.	29,339	—
Stockholders' equity:		
Common stock, $0.001 par value; 200,000,000 shares authorized, 82,283,693 and 72,201,505 shares issued and outstanding at December 31, 2006 and 2005, respectively	82	72
Additional paid-in capital	880,954	770,263
Accumulated other comprehensive income	4,278	3,178
Accumulated deficit	(816,751)	(770,848)
Total stockholders' equity	68,563	2,665
Total liabilities, noncontrolling interest and stockholders' equity	$ 255,907	$ 166,373

See accompanying notes.

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

	Years Ended December 31,		
	2006	2005	2004
Revenue:			
Research and development revenue under collaborative agreements	$ 15,091	$ 28,610	$ 32,617
Licensing and royalty revenue	9,441	11,523	10,007
Total revenue	24,532	40,133	42,624
Expenses:			
Research and development	80,567	82,467	118,474
Selling, general and administrative	12,619	8,432	9,582
Compensation benefit related to variable accounting of stock options	—	(544)	(6)
Restructuring activities	(536)	6,960	32,427
Total operating expenses	92,650	97,315	160,477
Loss from operations	(68,118)	(57,182)	(117,853)
Other income (expense):			
Investment income	5,960	5,094	2,999
Interest expense	(9,029)	(20,313)	(22,592)
Gain (loss) on investments, net	2,263	—	(5,057)
Net loss before noncontrolling interest in Symphony GenIsis, Inc.	(68,924)	(72,401)	(142,503)
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	23,021	—	—
Accretion of dividends on preferred stock	—	—	(361)
Net loss applicable to common stock	$(45,903)	$(72,401)	$(142,864)
Basic and diluted net loss per share	$ (0.62)	$ (1.15)	$ (2.52)
Shares used in computing basic and diluted net loss per share	74,308	62,877	56,642

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)
Years Ended December 31, 2006, 2005 and 2004
(In thousands)

Description	Preferred stock Shares	Preferred stock Amount	Preferred stock Dividend Accretion	Common stock Shares	Common stock Amount	Additional paid in capital	Deferred compensation	Accumulated other comprehensive income/(loss)	Accumulated deficit	Total stockholders' equity (deficit)
Balance at December 31, 2003	12	$ 12,015	$ 2,560	55,557	$56	$604,948	$(294)	$3,476	$(555,583)	$ 67,178
Comprehensive Loss:										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(142,864)	(142,864)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	(853)	—	(853)
Comprehensive loss	—	—	—	—	—	—	—	—	—	(143,717)
Dividends accrued on preferred stock	—	—	361	—	—	—	—	—	—	361
Deferred compensation	—	—	—	—	—	(228)	228	—	—	—
Options exercised and employee stock purchase plan	—	—	—	834	—	4,051	—	—	—	4,051
Compensation benefit relating to the granting of options	—	—	—	—	—	—	(6)	—	—	(6)
Conversion of preferred stock into common stock	(12)	(12,015)	(2,921)	1,056	1	14,935	—	—	—	—
Balance at December 31, 2004	—	$ —	$ —	57,447	$57	$623,706	$ (72)	$2,623	$(698,447)	$ (72,133)
Comprehensive Loss:										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(72,401)	(72,401)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	555	—	555
Comprehensive loss	—	—	—	—	—	—	—	—	—	(71,846)
Deferred compensation	—	—	—	—	—	61	16	—	—	77
Options exercised and employee stock purchase plan	—	—	—	254	1	989	—	—	—	990
Compensation benefit relating to the granting of options	—	—	—	—	—	(678)	56	—	—	(622)
Conversion of Lilly debt	—	—	—	2,500	2	99,998	—	—	—	100,000
Private Placement Offering	—	—	—	12,000	12	46,187	—	—	—	46,199
Balance at December 31, 2005	—	$ —	$ —	72,201	$72	$770,263	$ —	$3,178	$(770,848)	$ 2,665
Comprehensive Loss:										
Net loss applicable to common stock	—	—	—	—	—	—	—	—	(45,903)	(45,903)
Change in unrealized gains and (losses)	—	—	—	—	—	—	—	1,100	—	1,100
Comprehensive loss	—	—	—	—	—	—	—	—	—	(44,803)
Options exercised and employee stock purchase plan	—	—	—	1,883	2	11,518	—	—	—	11,520
Warrants exercised	—	—	—	229	—	—	—	—	—	—
Share-based compensation expense	—	—	—	—	—	5,747	—	—	—	5,747
Issuance of common stock under Azimuth equity financing	—	—	—	7,971	8	74,836	—	—	—	74,844
Issuance of warrants to Symphony Capital	—	—	—	—	—	18,590	—	—	—	18,590
Balance at December 31, 2006	—	$ —	$ —	82,284	$82	$880,954	$ —	$4,278	$(816,751)	$ 68,563

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Years Ended December 31,		
	2006	2005	2004
Operating activities:			
Net loss	$ (45,903)	$ (72,401)	$ (142,503)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation	3,854	5,817	8,401
Amortization of patents	1,633	1,545	1,442
Amortization of licenses	2,335	2,326	2,327
Amortization of (discount)/premium on investments, net	(606)	697	—
Share-based compensation expense	5,747	—	—
Compensation benefit related to variable accounting of stock options	—	(544)	(6)
Deferred interest on long-term debt	—	10,795	13,049
Loss attributed to noncontrolling interest in Symphony GenIsis, Inc.	(23,021)	—	—
(Gain)/Loss on investments	(2,263)	—	5,057
Non-cash restructuring activities	—	—	32,427
Non-cash losses related to patents and fixed assets	2,410	3,087	2,275
Income from variable accounting of stock warrants	—	(1,980)	—
Gain on disposal of property, plant and equipment	—	(1,455)	—
Changes in operating assets and liabilities:			
Contracts receivable	1,523	5,380	(7,391)
Inventory	90	1,771	(9,699)
Other current and long-term assets	(193)	(7)	1,373
Accounts payable	1,214	(4,872)	3,247
Accrued compensation	2,516	231	(674)
Accrued liabilities	(2,135)	406	1,711
Deferred contract revenues	(426)	(11,840)	(12,787)
Net cash used in operating activities	(53,225)	(61,044)	(101,751)
Investing activities:			
Purchase of short-term investments	(107,025)	(18,381)	(72,479)
Proceeds from the sale of short-term investments	72,575	51,029	176,147
Purchases of property, plant and equipment	(1,042)	(422)	(3,526)
Proceeds from the sale of property, plant and equipment	—	14,020	—
Acquisition of licenses and other assets	(1,514)	(2,451)	(6,411)
Strategic investments in corporate securities	—	—	(10,000)
Proceeds from the sale of strategic investments	4,397	3,283	—
Net cash provided by (used in) investing activities	(32,609)	47,078	83,731
Financing activities:			
Net proceeds from issuance of equity	86,364	49,168	4,051
Proceeds from long-term borrowing	—	4,603	24,470
Principal payments on debt and capital lease obligations	(7,851)	(16,170)	(16,368)
Proceeds from contribution to noncontrolling interest in Symphony GenIsis, Inc., net of fees	70,950	—	—
Net cash provided by financing activities	149,463	37,601	12,153
Net increase (decrease) in cash and cash equivalents	63,629	23,635	(5,867)
Cash and cash equivalents at beginning of year	50,885	27,250	33,117
Cash and cash equivalents (including cash and cash equivalents held by Symphony GenIsis, Inc. of $54.8 million, $0 and $0 at December 31, 2006, 2005 and 2004, respectively) at end of year	$ 114,514	$ 50,885	$ 27,250
Supplemental disclosures of cash flow information:			
Interest paid	$ 8,431	$ 8,877	$ 8,990
Warrant issued in conjunction with Symphony GenIsis, Inc. transaction	$ 18,590	$ —	$ —
Supplemental disclosures of non-cash investing and financing activities:			
Acquisition of property, plant and equipment	$ 361	$ —	$ —
Amounts accrued for capital and patent expenditures	$ 979	$ 397	$ 129
Conversion of receivables into long-term investment	$ —	$ 750	$ —
Conversion of debt into common stock	$ —	$ 100,000	$ —
Conversion of preferred stock into common stock	$ —	$ —	$ 14,934

See accompanying notes

1. Organization and Significant Accounting Policies

Basis of Presentation

The consolidated financial statements include the accounts of Isis Pharmaceuticals, Inc. and its wholly owned subsidiaries, Ibis Biosciences, Inc. ("Ibis"), Isis Pharmaceuticals Singapore Pte Ltd., Isis USA Limited, Hepasense, Ltd. and Orasense, Ltd. On July 25, 2005 and October 25, 2006, Isis dissolved the Hepasense, Ltd. and Orasense, Ltd. subsidiaries, respectively. As more fully described in *Note 8—Restructuring Activities,* Isis closed its Singapore operations in early 2005. In addition to its wholly owned subsidiaries, the 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 ("FIN") 46 (revised 2003), *Consolidation of Variable Interest Entities, an Interpretation of ARB 51.* All significant intercompany balances and transactions have been eliminated.

Organization and business activity

Isis Pharmaceuticals was incorporated in California on January 10, 1989. In conjunction with its initial public offering, Isis Pharmaceuticals was reorganized as a Delaware corporation, as Isis Pharmaceuticals, Inc. ("Isis"), in April 1991. Isis was organized principally to develop human therapeutic drugs using antisense and combinatorial technology.

Basic net loss per share

Isis follows the provisions of Statement of Financial Accounting Standards ("SFAS") 128, *Earnings per Share*. Isis computes basic loss per share by dividing the net loss applicable to common stock by the weighted average number of common shares outstanding during the period ("Basic EPS method"). Isis computes diluted loss per common share using the weighted-average number of common and dilutive common equivalent shares outstanding during the period ("Diluted EPS method"). Diluted common equivalent shares of 10.0 million at December 31, 2006 consisted of shares issuable upon exercise of stock options, warrants and convertible debt. As Isis incurred a loss in the years ended December 31, 2006, 2005 and 2004, Isis did not include diluted common equivalent shares in the computation of diluted net loss per share because the effect would be anti-dilutive.

Contract revenue and expenses

Contract revenue consists of non-refundable research and development funding and Isis records contract revenue as earned based on the performance requirements of Isis' collaborative research and development contracts. Isis recognizes contract revenue for which no further performance obligations exist when Isis receives the payments or when Isis is reasonably certain it can collect the receivable. Isis records payments received in excess of amounts earned as deferred contract revenue. Isis expenses research and development costs as incurred. For the years ended December 31, 2006, 2005 and 2004, research and development costs of approximately $13.6 million, $30.4 million, and $36.3 million, respectively, were related to collaborative research and development arrangements.

Revenue Recognition

Isis follows the provisions as set forth by Staff Accounting Bulletin ("SAB") 101, *"Revenue Recognition in Financial Statements,"* SAB 104, *"Revenue Recognition,"* and Financial Accounting Standards Board

Emerging Issues Task Force ("EITF") 00-21, "*Accounting for Revenue Arrangements with Multiple Deliverables.*"

Isis generally recognizes revenue when it has satisfied all contractual obligations and is reasonably assured of collecting the resulting receivable. Isis is often entitled to bill its customers and receive payment from our customers in advance of recognizing the revenue under current accounting rules. In those instances where Isis has billed its customers or received payment from its customers in advance of recognizing revenue, the amounts are included in deferred revenue on the balance sheet.

Research and development revenue under collaborative agreements

Isis often enters into collaborations where we receive non-refundable upfront payments for prior or future expenditures. Isis recognizes revenue related to upfront payments ratably over the period of the contractual arrangements as it satisfies its performance obligations. Occasionally, Isis is required to estimate the period of a contractual arrangement or its performance obligations when the agreements it enters 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.

Isis' collaborations often include contractual milestones. When it achieves these milestones, it is entitled to payment, as defined by the underlying agreements. Isis generally recognizes revenue related to milestone payments upon completion of the milestone's performance requirement, as long as it is reasonably assured of collecting the resulting receivable and we are not obligated for future performance related to the achievement of the milestone.

Isis generally recognizes revenue related to the sale of its drug inventory as it ships or delivers drugs to its partners. In several instances, Isis completed the manufacturing of drugs, but its partners asked them to deliver the drug on a later date. Under these circumstances, Isis ensured that their obligations were complete under the terms of the manufacturing agreement in place and title had transferred to the customer before it recognized the related revenue.

Isis often enters into revenue arrangements that contain multiple deliverables. In these cases, it recognizes revenue from each element of the arrangement as long as it is able to determine a separate value for each element, it has completed its obligation to deliver or perform on that element and it is reasonably assured of collecting the resulting receivable.

In the fourth quarter of 2006, Isis sold its first commercial Ibis T5000 Biosensor System. The sale of an Ibis T5000 Biosensor System contains multiple elements. Since Isis had no previous experience of commercially selling the Ibis T5000 Biosensor System, it had no basis to determine the fair values of the various elements included in the system; therefore, it must account for the entire system as one deliverable and recognize revenue over the entire period of performance. For a one-year period following the sale, Isis has ongoing support obligations for the Ibis T5000 Biosensor System, therefore it is amortizing the revenue for the entire system over a one-year period. Once Isis obtains a sufficient number of sales to enable it to identify each element's fair value, it will be able to recognize revenue separately for each element.

As part of Isis' Lilly alliance, in 2001 Lilly provided Isis a $100.0 million interest free loan to fund the companies' research collaboration. Isis 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 it 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 contractual performance. In August 2005, Isis converted the loan into 2.5 million shares of its common stock. Concurrent with the conversion, Isis extended the research collaboration.

Licensing and royalty revenue

Isis often enters into agreements to license its proprietary patent rights on an exclusive or non-exclusive basis in exchange for license fees and/or royalties. Isis generally recognizes as revenue immediately those licensing fees and royalties for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable.

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 commercial paper, debt instruments of financial institutions and corporations, certificates of deposit, money market funds, asset-backed securities and government-sponsored enterprises securities. Isis and its audit committee establish guidelines relative to credit ratings, diversification and maturities that seek to maintain safety and liquidity.

Cash, cash equivalents and short-term investments

Isis considers all liquid investments with maturities of ninety days or less when purchased to be cash equivalents. Isis' short-term investments have initial maturities of greater than ninety days from date of purchase. Isis classifies its securities as "available-for-sale" in accordance with SFAS 115, *Accounting for Certain Investments in Debt and Equity Securities.* Isis carries these investments at fair market value with any unrealized gains and losses recorded as a separate component of stockholders' equity. Fair value is based upon market prices quoted on the last day of the fiscal period. Isis uses the specific identification method to determine the cost of debt securities sold. Isis includes gross realized gains and losses 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 2006 and 2005, Isis sold a portion of its investment in Alnylam Pharmaceuticals, Inc. resulting in a realized gain of $2.7 million and $951,000, respectively. The $2.7 million realized gain on investments in 2006 was offset by a non-cash loss on investments of $465,000 related to the impairment of Isis' equity investment in Antisense Therapeutics Limited, which was recorded in the second quarter of 2006. In the second half of 2006, Isis recorded a net unrealized gain of $390,000 related to its equity investment in ATL as a separate component of stockholders' equity. This reflected the increase in the market value of the investment since the impairment in the second quarter of

2006. During the third quarter of 2004, Isis recorded a non-cash loss on investments of $5.1 million, principally related to the impairment of Isis' equity investment in Alnylam.

Inventory valuation

Isis includes in inventory material costs for drugs that Isis manufactures for its partners under contractual terms and that Isis uses primarily in its clinical development activities and drug products. Isis expenses these costs when it delivers its drugs to partners, or as it provides these drugs for its own clinical trials. Also included in inventory, as of December 31, 2006, are material costs and related manufacturing costs associated with the Ibis T5000 Biosensor System and related assay kits. 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 the 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 life 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 $861,000 and $951,000 as of December 31, 2006 and 2005, respectively.

Property, plant and equipment

Property, plant and equipment are stated at cost and consist of the following (in thousands):

	December 31,	
	2006	2005
Leasehold improvements	$ 11,758	$ 10,752
Equipment and computer software	22,761	21,895
Furniture and fixtures	1,533	1,533
	36,052	34,180
Less accumulated depreciation	(28,895)	(25,050)
	$ 7,157	$ 9,130

Depreciation of property, plant and equipment is provided on the straight-line method over estimated useful lives as follows:

Equipment	5 years
Computer software	3 years
Furniture and fixtures	5 years

Leasehold improvements are depreciated using the shorter of the estimated useful life or remaining lease term.

Licenses

Isis obtains licenses from third parties and capitalizes the costs related to exclusive licenses. Isis' license from Idera Pharmaceuticals, Inc., formerly Hybridon, Inc., comprised the majority of the license balance as of December 31, 2006 and 2005. Isis amortizes capitalized licenses over their estimated useful life or term of the agreement, which for current licenses is between approximately 8 years and 15 years. Accumulated amortization related to licenses was $14.5 million and $12.2 million at December 31, 2006

and 2005, respectively. Based on existing licenses, estimated amortization expense related to licenses is $2.3 million for each of the years ending December 31, 2007, 2008, 2009, 2010 and 2011.

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 Isis is not actively pursuing and writes off any of these costs, if appropriate. Isis amortizes patent costs over their estimated useful lives of 10 years, beginning with the date the patents are issued. The weighted average remaining life of issued patents was 4.6 years and 5.2 years at December 31, 2006 and 2005, respectively. In 2006 and 2005, Isis recorded a non-cash charge of $2.8 million and $1.7 million, respectively, which primarily is included in research and development expenses and is related to the write-down of its patent costs to their estimated net realizable values.

Accumulated amortization related to patents was $8.6 million and $7.0 million at December 31, 2006 and 2005, respectively. Based on existing patents, estimated amortization expense related to patents is as follows:

Years Ending December 31,	Amortization (in millions)
2007	$1.5
2008	$1.4
2009	$1.3
2010	$1.2
2011	$1.0

Investment in affiliates

In April 1999 and January 2000, Isis and Elan formed Orasense, Ltd. and Hepasense, Ltd., respectively, both Bermuda limited companies. Each joint venture was owned 80.1% by Isis and 19.9% by Elan. In 2002, Elan concluded its participation in both the Orasense and Hepasense collaborations. In June 2004, Isis acquired Elan's minority interest in Orasense and Hepasense. As a result, Isis owned 100% of Orasense and Hepasense at December 31, 2004. Isis dissolved the Hepasense and Orasense subsidiaries in July 2005 and October 2006, respectively.

Fair value of financial instruments

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

Long-lived assets

Isis periodically evaluates carrying values of long-lived assets including property, plant and equipment and intangible assets, when events and circumstances indicate that these assets may have been impaired. Isis has adopted SFAS 144, *Accounting for the Impairment of Long-Lived Assets*. Isis recorded a charge of $2.4 million, $15.6 million and $11.5 million for the years ended December 31, 2006, 2005 and 2004,

respectively, primarily related to the write-down of equipment and intangible assets to their estimated net realizable values.

Use of estimates

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

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 December 31, 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, ISIS 325568 and ISIS 377131. 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 included the financial condition and results of operations of Symphony GenIsis in its consolidated financial statements. *(Note 6—Collaborative Arrangements and Licensing Agreements).*

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 note. Isis expensed the payments when made. The 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 $1.0 million convertible note. The note will convert into securities that Sarissa issues in a financing. Isis has recognized a valuation allowance of $1.0 million to offset the note, 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 a $250,000 cash payment and a $250,000 convertible note. In December 2005, Isis entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo purchased 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. In December 2006, Isis' obligations under the manufacturing and supply agreement were completed and title of the product transferred to iCo. As a result, in January 2007, iCo paid Isis the remaining balance of $175,000. 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 it 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 employee stock purchase plan based on estimated fair values. SFAS 123R supersedes Isis' previous accounting under Accounting Principles Board Opinion ("APB") 25, *Accounting for Stock Issued to Employees* and SFAS 123, *Accounting for Stock-Based Compensation*, beginning January 1, 2006. In March 2005, the SEC issued SAB 107 relating to SFAS 123R. 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 fiscal year 2006. Isis' Consolidated Statements of Operations for the year ended December 31, 2006 reflects the impact of SFAS 123R. In accordance with the modified prospective transition method, Isis' 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' Consolidated Statements of Operations. For the year ended December 31, 2006, Isis' 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 Statement of Operations for the year ended December 31, 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 its stock option plans and employee stock purchase plan, 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 year ended December 31, 2006 was $5.7 million. The non-cash stock-based compensation benefit resulting from the 2003 option exchange program for the years ended December 31, 2005 and 2004 was $544,000 and $6,000, respectively.

In April 2003, Isis implemented an employee stock option exchange program ("2003 option exchange program"). The 2003 option exchange program allowed employees during the offering period, which began on April 8, 2003 and ended on May 8, 2003, to surrender options granted prior to January 5, 2002, which had higher exercise prices, in exchange for a lesser number of options, which had lower exercise prices. Employees exchanged 2.2 million options having a weighted-average exercise price of $14.89 for 1 million options having an exercise price of $5.15. The new options, fully vested as of January 31, 2006, and 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, *Accounting for Certain Transactions involving Stock Compensation—an interpretation of APB Opinion 25.* As a result, Isis recorded non-cash compensation expense/benefit related to stock options on its Consolidated Statements of Operations.

See *Note 4—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 display comprehensive loss and its components as part of Isis' full set of consolidated financial statements. The measurement and presentation of net loss did not change. Comprehensive loss is comprised of net loss and certain changes in equity that are excluded from net loss. Specifically, SFAS 130 requires unrealized holding gains and losses on Isis' available-for-sale securities, which Isis reports separately in stockholders' equity, to be included in accumulated other comprehensive loss. Comprehensive loss for the years ended December 31, 2006, 2005 and 2004 has been reflected in Isis' Consolidated Statements of Stockholders' Equity.

Segment information

Isis operates in two separate segments; Drug Discovery and Development and its Ibis Biosciences, Inc. subsidiary. In accordance with SFAS 131, *Disclosure about Segments of an Enterprise and Related Information*, Isis provides segment financial information and results for Drug Discovery and Development

and Ibis Biosciences based on the segregation of revenues and expenses used for management's assessment of operating performance and operating decisions. Expenses shared by the segments require the use of judgments and estimates in determining the allocation of expenses to the two segments. Different assumptions or allocation methods could result in materially different results by segment. 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.

Impact of recently issued accounting standards

In July 2006, the Financial Accounting Standards Board issued FIN 48, *Accounting for Uncertainty in Income Taxes*, which clarifies the accounting for uncertainty in income taxes recognized in a company's financial statements in accordance with SFAS 109, *Accounting for Income Taxes*. FIN 48 prescribes a recognition threshold and measurement attribute for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. FIN 48 will be effective for fiscal years beginning after December 15, 2006, and is required to be adopted by Isis in 2007. Isis does not expect the adoption of FIN 48 to have a material impact on its consolidated financial position, results of operations, or cash flows.

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. This Statement is effective for all financial statements issued for fiscal years that begin after November 15, 2007. Isis is currently evaluating the impact of adopting SFAS 157 to determine the effects, if any, on its operating results and financial position.

2. Investments

Isis invests its excess cash primarily in commercial paper and debt instruments of financial institutions and corporations with strong credit ratings as of December 31, 2006. Isis has established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to maximize trends in yields and interest rates without compromising safety and liquidity.

The following table summarizes the contract maturity of debt securities held by Isis as of December 31, 2006:

Less than 1 year	96%
1 - 2 years	4%
Total	100%

Isis has an ownership interest of less than 20% in each of two public and four private companies it conducts business with, and accounts for them under the cost method of accounting according to APB 18. The companies are Alnylam and ATL, which are publicly-traded, and Santaris Pharma A/S, OncoGenex Technologies, Inc., Achaogen and iCo, which are privately-held. In determining if and when decreases in market value of Isis' equity positions below their cost are other-than-temporary, Isis examines historical

trends in stock prices, the financial condition and near term prospects of the companies, and Isis' current need for cash. When Isis determines that a decline in value is other-than-temporary, Isis recognizes an impairment loss in the current period operating results to the extent of the decline. See *Note 1—Organization and Significant Accounting Policies* for a discussion of impairment losses incurred in 2006, 2005 and 2004.

The following is a summary of Isis' investments (in thousands):

December 31, 2006	Maturity in Years	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Available for sale securities:					
U.S. corporate debt securities	Less than 1	$71,361	$ 3	$ (9)	$71,355
Government-sponsored enterprises securities	Less than 1	2,998	—	(31)	2,967
Total short-term investments		74,359	3	(40)	74,322
Government-sponsored enterprises securities	1 to 2	4,526	—	(29)	4,497
Total long-term investments		4,526	—	(29)	4,497
Subtotal		$78,885	$ 3	$(69)	$78,819
Equity securities:					
Short-term portion		2,561	4,344	—	6,905
Long-term portion		2,125	—	—	2,125
Subtotal		$ 4,686	$4,344	$ —	$ 9,030
		$83,571	$4,347	$(69)	$87,849

December 31, 2005	Maturity in Years	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Available for sale securities:					
U.S. corporate debt securities	Less than 1	$15,549	$ 1	$ (28)	$15,522
Government-sponsored enterprises securities	Less than 1	20,543	—	(111)	20,432
Total short-term investments		36,092	1	(139)	35,954
U.S. corporate debt securities	1 to 2	185	—	(3)	182
Government-sponsored enterprises securities	1 to 3	7,552	—	(184)	7,368
Total long-term investments		7,737	—	(187)	7,550
Subtotal		$43,829	$ 1	$(326)	$43,504
Equity securities:					
Short-term portion		3,026	1,835	(167)	4,694
Long-term portion		3,806	1,835	—	5,641
Subtotal		$ 6,832	$3,670	$(167)	$10,335
		$50,661	$3,671	$(493)	$53,839

Investments considered to be temporarily impaired at December 31, 2006 are as follows (in thousands):

	Number of Investments	Less than 12 months of temporary impairment		Greater than 12 months of temporary impairment		Total temporary impairment	
		Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Available for sale securities:							
U.S. corporate debt securities	19	$47,267	$ 9	$ —	$—	$47,267	$ 9
Government-sponsored enterprises securities	6	—	—	7,464	92	7,464	92
Total temporarily impaired securities	25	$47,267	$ 9	$7,464	$92	$54,731	$101

Isis believes that the decline in value of these securities is temporary and primarily related to the change in market interest rates since purchase. Isis intends to hold these securities to maturity and anticipates full recovery of amortized cost with respect to these securities at maturity.

3. Long-Term Obligations and Commitments

Long-term obligations consisted of the following (in thousands):

	December 31,	
	2006	2005
Standard operating debt	13,951	20,158
5½% convertible subordinated notes	125,000	125,000
Capital leases and other obligations	1,385	2,592
Total	$140,336	$147,750
Less: current portion	(7,514)	(7,835)
Total Long-Term Obligations	$132,822	$139,915

Standard Operating Debt

In December 2003, Isis obtained a $32.0 million term loan from Silicon Valley Bank. The term loan is secured by substantially all of Isis' operating assets, excluding intellectual property, real estate, and certain equity investments. The term loan bears interest at the prime rate less applicable discounts (8.0% at December 31, 2006), is payable in monthly payments of principal and interest, matures in December 2008, and is convertible at the election of Isis to a fixed rate at the then-applicable prime rate plus 1.25%. The term loan is subject to certain liquidity and other covenants, including a requirement that Isis maintain a minimum balance in an account at the lending bank at all times equal to the outstanding balance of the loan. Isis was in compliance with these covenants as of December 31, 2006 and 2005. Isis used the proceeds of the loan to pay partner debt in 2004. The carrying value of this loan at December 31, 2006 and 2005 was $14.0 million and $20.2 million, respectively, which approximated fair value.

Convertible Subordinated Notes

In May 2002, Isis completed a $125.0 million convertible debt offering, which raised proceeds of approximately $120.9 million, net of $4.1 million in issuance costs. Isis includes the issuance costs in the

balance sheet under Deposits and Other Assets and is amortizing these issuance costs to interest expense over the life of the debt. The subordinated notes mature in 2009 and bear interest at 5½%, which is payable semi-annually. The notes are convertible, at the option of the note holders, into approximately 7.5 million shares of common stock at a conversion price of $16.625 per share. At both December 31, 2006 and 2005, the principal and accrued interest outstanding on the notes was $125.0 million and $1.1 million, respectively. The fair value of the subordinated notes was $126.9 million and $110.5 million as of December 31, 2006 and 2005, respectively. Isis did not include the effect of the conversion of these convertible notes into Isis' common stock in the computation of diluted net loss per share because the effect would have been anti-dilutive.

In January 2007, Isis completed a $162.5 million convertible debt offering, which raised proceeds of approximately $157.0 million, net of $5.5 million in issuance costs. The $162.5 million convertible subordinated notes mature in 2027 and bear interest at 2⅝%, which is payable semi-annually.

The 2⅝% notes are convertible, at the option of the note holders, into approximately 11.1 million shares of common stock at a conversion price of approximately $14.63 per share. Isis will be able to redeem the 2⅝% notes at a redemption price equal to 100.75% of the principal amount between February 15, 2012 and February 14, 2013; 100.375% of the principal amount between February 15, 2013 and February 14, 2014; and 100% of the principal amount thereafter. Holders of the 2⅝% notes will also be able to require Isis to repurchase these notes on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100% of the principal amount of the 2⅝% notes being repurchased plus accrued interest and unpaid interest. Through privately negotiated transactions, Isis has repurchased approximately $44.1 million aggregate principal amount of the total outstanding of its 5½% convertible subordinated notes. Isis intends to use the remaining net proceeds of the 2⅝% notes to repurchase the remaining portion of its existing 5½% notes.

Capital Leases and Other Obligations

At December 31, 2006 and 2005, Isis had approximately $1.0 million and $2.4 million outstanding, respectively, under various capital equipment leases, which bear interest at rates ranging from 7.25% to 8.78% and mature at various dates through 2008. As of December 31, 2006 and 2005, Isis had approximately $378,000 and $160,000, respectively, under various contractual obligations. *(Note 11—Legal Proceedings and Note 6—Collaborative Arrangements and Licensing Agreements).*

Annual debt and other obligation maturities at December 31, 2006 are as follows (in thousands):

2007	$ 7,514
2008	7,446
2009	125,001
2010	1
2011	1
Thereafter	373
Total	$140,336

Isis leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through September 2020. The lease for the building that houses Ibis expires in 2010 and has two five-year options to extend the lease. The lease on the building Isis primarily uses for laboratory and office space for its drug development business expires in 2012 and has a five-year option to extend the lease. In connection with the sale of its 28,704 square foot manufacturing facility in 2005, Isis leased back the facility for an initial term of fifteen years with an initial rent of $2.60 per rentable square foot. Under the terms of the lease, the monthly rent will increase five percent every two years. The future contractual obligations of this lease are included in the operating lease caption below. The lease provides Isis an option to extend the lease for up to two five-year periods. In connection with the lease, Isis executed a stand by letter of credit for $500,000. Annual future minimum payments under capital and operating leases as of December 31, 2006 are as follows (in thousands):

	Operating Leases	Capital Leases
2007	$ 2,857	$ 869
2008	2,769	190
2009	2,741	—
2010	2,282	—
2011	1,939	—
Thereafter	10,133	—
Total minimum payments	$22,721	1,059
Less amount representing interest		(51)
Present value of future minimum payments		1,008
Less current portion		(820)
Long-term portion		$ 188

Rent expense for the years ended December 31, 2006, 2005, and 2004 was $3.2 million, $2.6 million, and $3.1 million, respectively. Cost of equipment under outstanding capital leases at December 31, 2006 and 2005 was approximately $3.2 million and $5.1 million, respectively. Accumulated depreciation of equipment under outstanding capital leases at December 31, 2006 and 2005 was approximately $2.5 million and $3.1 million, respectively.

4. Stockholders' Equity

Preferred Stock

Isis is authorized to issue up to 15,000,000 shares of "blank check" Preferred Stock. As of December 31, 2006 and 2005, there were no shares of Isis' Series A Convertible Exchangeable 5% Preferred Stock or Series B Convertible Exchangeable 5% Preferred Stock outstanding. Series C Junior Participating Preferred Stock is designated but not outstanding.

Series C Junior Participating Preferred Stock

In December 2000, Isis adopted a Preferred Share Purchase Rights Plan ("Plan"). The Plan provides for a dividend distribution of one preferred stock purchase right ("Right") for each outstanding share of Isis common stock, par value $0.001 per share ("Common Shares"), held of record at the close of business on January 10, 2001, and on each subsequently issued share of Isis common stock. The Rights are not

currently exercisable. Under certain conditions involving an acquisition or proposed acquisition by any person or group holding 20% or more of Isis' common stock, the Rights permit the holders (except the 20 percent holder) to purchase one one-hundredth of a share of Series C Junior Preferred Stock, par value $0.001 per share ("Preferred Shares"), at a price of $85 per one one-hundredth of a Preferred Share, subject to adjustment. Each one one-hundredth of a share of Preferred Shares has designations and powers, preferences and rights, and qualifications, limitations and restrictions that make its value approximately equal to the value of a Common Share. Certain conditions allow the Isis Board of Directors to redeem the Rights in whole, but not in part, at a price of $0.001 per Right.

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. At December 31, 2006 and 2005, Isis had 200,000,000 shares and 100,000,000 shares, respectively, of common stock authorized, of which 82,283,693 and 72,201,505 were issued and outstanding, respectively. As of December 31, 2006, total common shares reserved for future issuance was approximately 21,924,862.

During 2006 and 2005, Isis issued 1.9 million and 254,000 shares of common stock, respectively, for stock option exercises and ESPP purchases. The net proceeds received from these transactions were $11.5 million and $991,000 in 2006 and 2005, respectively.

The common stock issued and outstanding includes 12 million shares of common stock issued in August 2005: Isis raised $51 million in a private placement of 12 million shares of its common stock at a price of $4.25 per share, which was a 2.3% discount from Isis' 60-day average trading price. Investors in the financing also received five-year warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.2395 per share. The net proceeds from the offering were $48.2 million. During 2006, Isis issued 229,000 shares of common stock for exercises of these warrants.

In August 2005, Isis converted its $100.0 million Lilly loan into 2.5 million shares of Isis' common stock. The impact to the balance sheet was a reduction in long term debt and an increase in stockholders' equity.

In May 2006, Isis entered into a Common Stock Purchase Agreement with Azimuth Opportunity Ltd. During the second half of 2006, Azimuth purchased approximately 8.0 million shares of Isis' common stock for $75.0 million at a weighted average price of $9.41 per share. Deducting transaction fees, Isis received net proceeds of $74.9 million.

Stock Option Plans

1989 Stock Option Plan and Other Employee Option Grants

In June 1989 and as amended, Isis' Board of Directors adopted, and the stockholders subsequently approved, a stock option plan that 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. The 1989 Plan does not allow Isis to grant stock bonuses or restricted stock awards and prohibits Isis from repricing any options outstanding under the plan unless Isis' stockholders approve the repricing. 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. At December 31, 2006, a total of 5,186,631 options were outstanding, options to purchase 2,297,379 shares were exercisable, and 2,495,456 shares were available for future grant under the 1989 plan.

2000 Broad Based Equity Incentive Plan

In January 2000, Isis adopted the 2000 Broad-Based Equity Incentive Plan (the "2000 Plan"), which provides for the issuance of non-qualified stock options for the purchase of up to 3,990,000 shares of common stock to its employees, directors, and consultants. In May 2002, Isis' Board of Directors increased the 2000 Plan by 2,000,000 shares, authorizing up to 5,990,000 shares of common stock under the 2000 Plan for issuance to employees, directors, and consultants. Typically options expire 10 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 or service as a consultant, employee or director. At December 31, 2006, a total of 2,102,436 options were outstanding, 2,004,775 shares were exercisable, and 2,201,431 shares were available for future grant under the 2000 Plan.

Change of Control Under 1989 Plan and 2000 Plan

With respect to both the 1989 Plan and 2000 Plan, in the event of:

- a sale, lease or other disposition of all or substantially all of its assets;
- a merger or consolidation in which Isis is not the surviving corporation; or
- reverse merger in which Isis is the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise,

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan and the 1989 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the shareholders in the transaction for those outstanding under the 2000 Plan and the 1989 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan and the 1989 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, such stock awards automatically vest in full (and, if applicable, the time during which such stock awards may be exercised) and the stock awards will terminate if not exercised (if applicable) at or prior to such event. With respect to any other stock awards outstanding under the 2000 Plan and the 1989 Plan, such stock awards will terminate if not exercised (if applicable) prior to such event. As of December 31, 2006, options to purchase approximately 97,661 shares granted under the 2000 Plan will be accelerated in full if a transaction described above occurs, even if the surviving corporation assumes such award.

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 10 years from the date of grant. Options granted become exercisable in four equal annual installments beginning one year after the date of grant. At December 31, 2006, a total of 367,000 options were outstanding, 199,500 of the shares issued under this plan were exercisable and 374,000 shares were available for future grant.

Employee Stock Purchase Plan

In 2000, Isis' Board of Directors adopted, and the stockholders subsequently approved, the 2000 Employee Stock Purchase Plan ("ESPP") and Isis reserved 200,000 shares of common stock for issuance thereunder. 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 as of December 31, 2006. 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 purchase period or the end of each six-month purchase period. During 2006, 150,890 shares were purchased and issued under this plan to employees at prices ranging from $3.36 to $4.45 per share. At December 31, 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 year ended December 31, 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	2,272	$5.89		
Exercised	(1,732)	$6.30		
Cancelled/forfeited/ expired	(863)	$8.44		
Outstanding at December 31, 2006	7,656	$7.57	5.04	$30,991
Exercisable at December 31, 2006	4,502	$8.74	4.28	$14,444

The following table summarizes information concerning outstanding and exercisable options as of December 31, 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	712	4.83	$ 4.76	428	$ 4.83
$5.25 - $5.25	1,345	6.01	$ 5.25	4	$ 5.25
$5.35 - $6.25	1,354	5.54	$ 5.85	533	$ 5.84
$6.29 - $6.81	1,635	4.86	$ 6.78	1,405	$ 6.79
$6.84 - $9.63	1,392	5.51	$ 8.12	965	$ 8.35
$9.75 - $22.83	1,218	3.25	$14.10	1,167	$14.18
	7,656	5.04	$ 7.57	4,502	$ 8.74

The weighted-average estimated fair values of options granted were $3.44 and $3.62 for the years ended December 31, 2006 and 2005, respectively. The total intrinsic value of options exercised during the years ended December 31, 2006, 2005 and 2004 were $6.6 million, $20,000 and $1.2 million, respectively, which was determined as of the date of exercise. The amount of cash received from the exercise of stock options were $10.9 million, $147,000 and $2.5 million for the years ended December 31, 2006, 2005 and 2004, respectively. For the year-ended December 31, 2006, the weighted-average fair value of options exercised was $10.11 As of December 31, 2006, there was $6.3 million of total unrecognized compensation cost related to non-vested stock-based compensation plans. Total unrecognized compensation cost will be adjusted for future changes in estimated forfeitures. Isis expects to recognize that cost over a weighted average period of 1.2 years.

The following table summarizes stock option activity under SFAS 123 for the years ended December 31, 2004 through December 31, 2005 (in thousands, except per share data):

	Number of Shares	Price Per Share	Weighted Average Price Per Share
Outstanding at December 31, 2003	8,211	$3.12 to $26.65	$8.66
Granted	2,163	$ 4.30 to $9.50	
Exercised	(508)	$ 3.12 to $8.15	
Terminated	(1,199)	$3.75 to $22.19	
Outstanding at December 31, 2004	8,667	$3.12 to $26.65	$8.34
Granted	1,571	$ 2.86 to $5.90	
Exercised	(32)	$ 3.12 to $5.15	
Terminated	(2,227)	$3.12 to $26.65	
Outstanding at December 31, 2005	7,979	$2.86 to $22.83	$7.86

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 year ended December 31, 2006 (in thousands, except per share data), which was allocated as follows:

	Year Ended December 31, 2006
Research and development	$4,541
Selling, general and administrative	1,206
Non-cash compensation expense related to stock options included in operating expenses	$5,747
Basic and diluted net loss per share	$ 0.08

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.

Had Isis determined compensation expense consistent with SFAS 123, it would have reported the following pro forma amounts for net loss applicable to common stock and basic and diluted net loss per share (in thousands, except per share amounts) for the years ended December 31, 2005 and 2004:

	Year Ended December 31, 2005	Year Ended December 31, 2004
Net loss applicable to common stock—as reported	$(72,401)	$(142,864)
Net loss applicable to common stock—pro forma	$(76,660)	$(148,994)
Basic and diluted net loss per share—as reported	$ (1.15)	$ (2.52)
Basic and diluted net loss per share—pro forma	$ (1.22)	$ (2.63)

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' 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 years ended December 31, 2006, 2005 and 2004:

Employee Stock Option Plans:

	December 31,		
	2006	2005	2004
Risk-free interest rate	4.9%	4.1%	3.0%
Dividend yield	0.0%	0.0%	0.0%
Volatility	68.6%	81.7%	94.4%
Expected Life	4.6 years	4.8 years	4.8 years

2002 Plan:

	December 31,		
	2006	2005	2004
Risk-free interest rate	5.1%	4.2%	3.4%
Dividend yield	0.0%	0.0%	0.0%
Volatility	85.2%	70.7%	94.9%
Expected Life	7.0 years	4.8 years	4.8 years

ESPP:

	December 31,		
	2006	2005	2004
Risk-free interest rate	4.8%	3.8%	4.2%
Dividend yield	0.0%	0.0%	0.0%
Volatility	49.9%	53.4%	57.2%
Expected Life	6 months	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 other two 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 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.

Warrants

In 2002, Isis issued a warrant to purchase 6,304 shares of common stock to Elan for the achievement of a development milestone related to the Hepasense joint venture between Isis and Elan. As of December 31, 2006, this warrant remained outstanding at an exercise price of $59.48 per share. The warrant expires April 25, 2007.

In connection with the August 2005 private placement financing, investors received five-year warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.2395 per share. The warrants issued in the private placement provide a call right in favor of Isis to the extent that the price per share of Isis' common stock exceeds $14.41 per share for twenty (20) consecutive trading days, subject to certain circumstances. Isis cannot exercise this call right prior to August 2008. As of December 31, 2006, 2.5 million shares of common stock under the warrants remained outstanding.

Prior to the registration statement for the August private placement financing becoming effective, the potential existed for Isis to pay liquidated damages if such effectiveness did not occur. Accordingly, as required by EITF 00-19, *"Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock,"* Isis periodically revalued the Warrants as a derivative instrument by computing the value in connection with changes in the underlying stock price and other assumptions, with the change in value recorded as interest expense or interest income. Before November 1, 2005, the effective date of the underlying registration statement, the warrant liability was recorded at fair value, which was determined using the Black-Scholes option-pricing model. Changes in fair value during each period were recorded as interest income. On November 1, 2005, the effective date of the underlying registration statement, the warrant liability was reclassified into stockholders' equity.

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

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

exchange ratio reflecting the total consideration paid by the surviving entity at the time of such change in control, as if the total consideration (including cash) for each share of Isis' common stock was instead paid only in Public Common Shares of the surviving entity at the time of such change of control; or

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

5. Income Taxes

Significant components of Isis' deferred tax assets as of December 31, 2006 and 2005 are shown below (in thousands). Isis recognized valuation allowances of $288.5 million and $270.5 million for 2006 and 2005, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	2006	2005
Deferred tax assets:		
Capitalized research expense	$ 35,497	$ 40,465
Net operating loss carryforwards	203,675	185,788
Research and development credits	38,096	36,782
Deferred revenue	930	617
Accrued restructuring	10,888	9,213
Other, net	5,068	6,537
Total deferred tax assets	294,154	279,402
Deferred tax liabilities:		
Intangible assets	(5,689)	(8,907)
Total deferred tax liabilities	(5,689)	(8,907)
Total net deferred tax assets	288,465	270,495
Valuation allowance for deferred tax assets	(288,465)	(270,495)
Net deferred tax assets	$ —	$ —

At December 31, 2006, approximately $10 million of tax benefit related to stock option deductions, when recognized, will be allocated directly to additional paid-in capital.

At December 31, 2006, Isis had federal, foreign and California tax net operating loss carryforwards of approximately $560.0 million, $1.0 million and $179.5 million, respectively. Isis also had federal and California research credit carryforwards of approximately $25.7 million and $18.5 million, respectively. The difference between the tax loss carryforwards for federal and California purposes is attributable to the capitalization of research and development expenses for California tax purposes and a required 50% to 60% limitation on the utilization of prior years California loss carryforwards. Unless previously utilized, the expiration of the federal tax loss carryforwards begins in 2007. The research credit carryforwards began expiring in 2007. The foreign tax losses may be carried forward indefinitely and used to offset future taxable profits, provided there is no substantial change in ownership. The California tax loss carryforwards began expiring in 2007.

Pursuant to Sections 382 and 383 of the Internal Revenue Code, annual use of Isis' net operating loss and credit carryforwards may be limited due to cumulative changes in ownership of more than 50%. Isis believes that changes in ownership have occurred, but believes that such limitations will not have a material impact upon the utilization of the carryforwards.

As a result of the adoption of SFAS 123R Isis recognizes excess tax benefits associated with the exercise of stock options directly to stockholders' equity only when realized. Accordingly, deferred tax assets are not recognized for net operating loss carryforwards resulting from excess tax benefits occurring from January 1, 2006 onward. At December 31, 2006, deferred tax assets do not include $7.0 million of excess tax benefits from share based compensation.

6. Collaborative Arrangements and Licensing Agreements

Antisense Drug Discovery Collaborations

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 ISIS 325568, targeting glucagon receptor ("GCGR"), and ISIS 377131, targeting glucocorticoid receptor ("GCCR"). 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 the development of ISIS 325568 and ISIS 377131 through initial proof-of-concept in human clinical trials. In addition to providing the financial support to move these three drugs forward, the transaction allows Isis to continue to control and manage the development of these 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 Isis. Isis licensed to Symphony GenIsis the intellectual property for its apoB-100, GCGR and GCCR programs. Isis has received an exclusive purchase option from Symphony GenIsis' investors that will allow it 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 structuring and legal fees of $4.1 million. Using a Black-Scholes option-pricing model, Isis 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 Isis is the primary beneficiary. As a result, Isis includes the financial condition and results of operations of Symphony GenIsis in Isis' consolidated financial statements. Isis' consolidated financial statements include the cash and cash equivalents held by Symphony GenIsis. Additionally, the consolidated financial statements include line items called "Noncontrolling interest in Symphony GenIsis." On the 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 was $23.0 million for the year ended December 31, 2006, until the balance becomes zero. The reductions to the "Noncontrolling Interest in Symphony GenIsis" on the Consolidated Balance Sheet are also recognized in Isis' Consolidated Statements of Operations using a similar caption and reduces Isis' net loss applicable to common stock. For the year ended December 31, 2006, Isis' net loss was reduced by $23.0 million.

The Ludwig Institute; Center for Neurological Studies

In October 2005, Isis entered a collaboration agreement with the Ludwig Institute, the Center for Neurologic Study (CNS) and researchers from these institutions to discover and develop antisense drugs in the areas of amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases. Under this agreement, Isis agreed to pay the Ludwig Institute and CNS royalties and modest milestones on any antisense drugs discovered and developed within the collaboration. The researchers from the Ludwig Institute and CNS, through funding from the ALS Association, will conduct preclinical safety and efficacy studies of ISIS 333611.

Pfizer, Inc.

In May 2005, Isis entered into a multi-year drug discovery collaboration with Pfizer to identify second generation antisense drugs for the treatment of ophthalmic disease. Under the terms of the agreement, Isis received a technology access fee of $1.0 million. To date, Isis has earned milestone payments totaling $1.2 million under the collaboration. Pfizer will also pay Isis additional milestone payments if key research, clinical, regulatory and sales milestones are achieved, and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug for the first indication, Isis will earn milestone payments totaling up to $26.1 million. In addition, Isis will receive royalties on the sale of drugs resulting from the collaboration.

Singapore Economic Development Board

In November 2003, Isis received a grant of up to $8.0 million over three years from the Singapore Economic Development Board ("Singapore EDB"), which was intended to fund, in part, the broadening of two of Isis' RNA-based drug discovery and development programs: MicroRNA drug discovery and antisense drug discovery targeting the coronavirus associated with SARS. In connection with this grant, Isis established Isis Pharmaceuticals Singapore Pte Ltd, a wholly owned subsidiary of Isis Pharmaceuticals, Inc. During 2004, Isis earned revenue of $1.5 million from this grant.

As part of Isis' reorganization, Isis decided to close its research and development laboratory in Singapore during the first quarter of 2005 and terminate its agreement with the Singapore EDB. Isis received $1.5 million in cash payments under this $8.0 million grant from the Singapore EDB and does not anticipate any additional payments, or additional revenue, under the agreement.

Amgen

In December 2001, Isis entered into a three-year collaboration with Amgen, Inc. to discover new antisense drugs. Amgen had the right to develop and commercialize antisense drugs resulting from the collaboration. Under the terms of the agreement, Isis was entitled to receive milestone payments upon key clinical, research and commercial achievements, as well as royalties on sales of any products resulting from the collaboration. During 2004, Isis earned revenue of $783,000 related to quarterly research support and progress research milestones under this drug discovery collaboration. In December 2004, Isis' collaboration with Amgen ended in accordance with its terms.

Eli Lilly and Company

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

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

As part of the collaboration, Lilly licensed LY2181308, Isis' antisense inhibitor of survivin and LY2275796, an antisense inhibitor of eIF-4E. To date, Isis has earned $4.1 million and $1.5 million in license fees and milestone payments related to the continued development of LY2181308 and LY2275796, respectively. Isis will receive additional milestone payments aggregating up to $25.0 million and $19.5 million if LY2181308 and LY2275796, respectively, achieve specified regulatory and commercial milestones, and royalties on future product sales of these drugs.

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

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

Merck & Co., Inc.

In June 1998, Isis entered into a multi-year research collaboration and licensed agreement with Merck to discover small molecule drug candidates to treat patients infected with HCV. The research collaboration ended in May 2003 in accordance with its terms. However, in December 2006, Merck advanced a drug discovered in this collaboration into Phase 1 clinical trials for which Isis received a $1 million milestone payment. In addition, Merck will pay Isis aggregate milestone payments of up to $16 million upon the achievement of key clinical and regulatory milestones, and royalties on future product sales.

Satellite Company Drug Discovery and Development Collaborations

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. In exchange for the exclusive, worldwide license to Isis' aminoglycoside program, Achaogen issued to Isis $1.5 million of Achaogen Series A Preferred stock. Isis has recognized a valuation allowance of $1.5 million to offset this asset as realization of this asset is uncertain. 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.

Antisense Therapeutics Limited

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

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

In connection with this collaboration, Isis received 30.0 million shares of ATL common stock upon completion of ATL's initial public offering ("IPO"), representing an initial ownership percentage of approximately 14%, and options to purchase an additional 20.0 million shares of ATL common stock, which expired in 2006. Isis valued its initial ownership at $2.8 million, and is recognizing revenue based on this amount over the term of the agreement. For the years ended December 31, 2006, 2005, and 2004, Isis recorded revenue of $652,000, $698,000, and $1.4 million, respectively, related to this collaboration. As of December 31, 2006, Isis' ownership percentage in ATL, including 10.3 million shares Isis purchased subsequent to shares it acquired in the IPO, was less than 10%. Isis' balance sheets at December 31, 2006 and 2005 included a short-term investment at fair market value of $1.3 million and $1.2 million, respectively, related to this equity investment.

Atlantic Healthcare (UK) Limited

In March 2007, Isis licensed alicaforsen to Atlantic Healthcare (UK) Limited, a UK-based company that was founded in 2006 by gastrointestinal drug developers to develop alicaforsen for the treatment of ulcerative colitis and other inflammatory diseases. Atlantic Healthcare plans to initially develop alicaforsen for pouchitis, an ulcerative colitis indication, followed by ulcerative colitis and other inflammatory diseases. In exchange for the exclusive, worldwide license to alicaforsen, Isis will receive an upfront payment from Atlantic Healthcare in the form of equity valued at $2 million. In addition, assuming Atlantic Healthcare successfully develops and commercializes alicaforsen, Isis will receive milestone payments and royalties on future product sales of alicaforsen. If Atlantic Healthcare meets certain of these milestones, at Atlantic Healthcare's request, Isis will attempt to identify a second generation lead drug candidate for Atlantic Healthcare. Atlantic Healthcare may take an exclusive worldwide license to the lead candidate under the terms and conditions of the agreement. Atlantic Healthcare is solely responsible for the continued development of alicaforsen, and, if selected, the second generation lead drug candidate.

iCo Therapeutics, Inc.

In August 2005, Isis granted a license to iCo for the development and commercialization of iCo 007, a second generation antisense drug. iCo is initially developing iCo 007 for the treatment of various eye diseases caused by the formation and leakage of new blood vessels, such as diabetic macular edema and diabetic retinopathy. iCo paid Isis a $500,000 upfront fee consisting of $250,000 in cash and a $250,000 convertible note. iCo will also pay Isis milestone payments totaling up to $23.0 million for the achievement of clinical and regulatory milestones. In addition, Isis will receive royalties on any product sales of this drug. Under the terms of the agreement, iCo is solely responsible for the clinical development and commercialization of the drug. In December 2006, iCo filed an IND application with the FDA for iCo 007 for which Isis earned a milestone payment.

In December 2005, Isis entered into a manufacturing and supply agreement with iCo. Under the agreement, iCo purchased 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. Isis has recognized a valuation of $600,000 to offset the convertible notes and the resulting common stock of iCo as the realization of this asset is uncertain. In December 2006, Isis' obligations under the manufacturing and supply agreement were completed and title of the product transferred to iCo. As a result, in January 2007, iCo paid Isis the remaining balance of $175,000. In May 2006, Isis received 869,025 shares of iCo common stock for the conversion of both convertible notes.

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.

OncoGenex Technologies Inc.

In November 2001, Isis established a drug development collaboration with OncoGenex, a biotechnology company committed to the development of cancer therapeutics for patients with drug

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

In September 2003, the companies expanded their antisense drug development partnership to include the development of the second generation antisense anti-cancer drug, OGX-225. OncoGenex is responsible for the preclinical and clinical development of the drug. OncoGenex issued to Isis OncoGenex securities as payment for an upfront fee. In addition, OncoGenex will pay Isis milestone payments totaling up to $3.5 million for the achievement of clinical and regulatory milestones, and pay Isis royalties on product sales. As of December 31, 2006, OncoGenex had not triggered any of these milestone payments related to OGX-225.

In January 2005, Isis further broadened its antisense drug development partnership with OncoGenex to allow for the development of two additional second generation antisense anti-cancer drugs. Under the terms of the agreement, OncoGenex is responsible for the preclinical and clinical development of the drugs. In April 2005, OncoGenex selected its first drug under this expansion, OGX-427. OGX-427 targets heat shock protein 27, or Hsp27, which is over-expressed in numerous tumor types and is associated with treatment resistance through its ability to help cancer cells survive stress-induced injury. OncoGenex paid Isis an upfront fee with a convertible note, which, in August 2005, converted into 244,300 shares of OncoGenex's preferred stock. OncoGenex will also pay Isis milestone payments totaling up to $5 million for the achievement of key clinical and regulatory milestones, and royalties on future product sales of these drugs.

For the years ended December 31, 2006, 2005 and 2004, Isis earned revenue of $1.2 million, $2.7 million and $669,000, respectively, related to its collaboration with OncoGenex. Isis' balance sheets at December 31, 2006 and 2005 include a long-term investment of $1.5 million related to Isis' equity investment in OncoGenex. While there is no readily determinable market value for these securities, there has been no indication that Isis' investment in OncoGenex has been impaired; accordingly, Isis believes that the carrying value of this investment is equal to or below its current fair market value.

Sarissa, Inc.

In February 2005, Isis licensed an anti-cancer antisense drug to Sarissa, Inc., a biotechnology company emerging from the University of Western Ontario. The drug is an antisense inhibitor of thymidylate synthase, or TS, a drug target that protects cancer cells from the effects of several chemotherapy treatments. In preclinical studies, antisense inhibition of TS suppressed human tumor cell growth and overcame tumor cell resistance to marketed TS-targeted drugs.

Under the terms of the agreement, Sarissa paid Isis a $1.0 million upfront fee in exchange for the exclusive, worldwide license to the TS antisense drug. Sarissa paid the upfront fee with a convertible note,

which will convert into Sarissa stock upon Sarissa's successful completion of a venture capital financing. Isis has recognized a valuation allowance of $1.0 million to offset the note as realization of this asset is uncertain. Sarissa will also pay Isis milestone payments totaling up to $5.5 million for the achievement of clinical and regulatory milestones. In addition, Isis will receive royalties on any sales of the TS antisense drug. Sarissa is solely responsible for preclinical and clinical development of the drug.

Satellite Company Technology Research Collaborations

Alnylam Pharmaceuticals, Inc.

In March 2004, Isis entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, Isis exclusively licensed to Alnylam its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5.0 million technology access fee, participation in fees for Alnylam's partnering programs, as well as future milestone and royalty payments from Alnylam. For each drug developed by Alnylam under this alliance, the potential milestone payments from Alnylam total $3.4 million and are payable to Isis upon the occurrence of specified development and regulatory events. Isis retained rights to a limited number of double-stranded RNAi therapeutic targets and all rights to single-stranded RNAi therapeutics. Isis also made a $10 million equity investment in Alnylam.

In turn, Alnylam nonexclusively licensed to Isis Alnylam patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry to research, develop and commercialize single-stranded RNAi therapeutics and to research double-stranded RNAi compounds. Isis also received a license to develop and commercialize double-stranded RNAi drugs targeting a limited number of therapeutic targets on either an exclusive or co-exclusive basis depending on the target. If Isis develops or commercializes an RNAi-based drug using Alnylam's technology, Isis will pay Alnylam milestones and royalties. For each drug, the potential milestone payments to Alnylam total $3.4 million and are payable by Isis upon the occurrence of specified development and regulatory events. As of December 31, 2006, Isis did not have an RNAi-based drug in clinical development. As part of the collaboration, each party granted the other party a nonexclusive cross license to its respective patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for microRNA therapeutics.

Isis' Alnylam alliance provides it with an opportunity to realize substantial value from its pioneering work in antisense mechanism and oligonucleotide chemistry and is an example of Isis' strategy to participate in all areas of RNA-based drug discovery. To date, Isis has earned approximately $5.0 million from Alnylam resulting from sublicenses of Isis' technology for the development of RNA interference therapeutics that Alnylam has granted to pharmaceutical partners.

In September 2004, Isis recorded a non-cash loss on investment of $5.0 million related to the impairment of its equity investment in Alnylam. The loss on investment reflected a decrease in the market value of Alnylam's stock in 2004, which Isis believes was primarily a result of financial market conditions related to biotechnology companies. Alnylam's stock is currently trading significantly above its 2004 levels, which we believe reflects Alnylam's leading position in the field of RNAi. Isis' balance sheets at December 31, 2006 and 2005, included a short-term investment at carrying value of approximately $5.6 million and $3.5 million, respectively, and a long-term investment of $3.5 million at December 31, 2005. During 2006 and 2005, Isis sold a portion of its Alnylam stock for cash proceeds of $4.4 million and $2.6 million, respectively. Isis held approximately 290,000 shares and 580,000 shares of Alnylam's stock at December 31, 2006 and 2005, respectively.

During 2006, 2005 and 2004, Isis generated revenue from its relationship with Alnylam totaling $750,000, $3.7 million and $5.5 million, respectively, representing 3%, 9% and 13%, respectively, of Isis' total revenue.

Ercole Biotech, Inc.

In May 2003, Isis and Ercole initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. Part of this collaboration includes a cross-license of Isis' respective splicing-related intellectual property with Ercole. Isis is combining its alternative splicing expertise with Ercole to discover antisense drugs that regulate alternative RNA splicing. As part of this collaboration, Isis granted Ercole a license to Isis' Bcl-x molecule and certain of its chemistry patents. In addition, Isis took an equity ownership position in Ercole with the initial funding, in the form of a convertible note, which the companies anticipate will convert into securities that Ercole issues in its next venture capital financing. Isis also has the option to make an additional equity investment in Ercole. Pursuant to the terms of a Note and Warrant Purchase Agreement, during 2003 and early 2004, Isis made cash payments to Ercole of $500,000 and $250,000, respectively in exchange for a convertible note. Isis expensed the payments when made. The note is secured by all of Ercole's assets, including intellectual property and licenses. The note will convert into securities that Ercole issues in a qualified financing, as defined by the agreement.

Rosetta Genomics, Ltd.

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.

Santaris Pharma A/S (formerly Pantheco A/S)

In November 1998 and September 2000, Isis entered into license agreements with Santaris, formerly Pantheco. Isis amended and restated the agreement in May 2003. Under the terms of the amended and restated license agreements, Isis licensed its novel antisense chemistry, Peptide Nucleic Acid, or PNA, to Santaris on a limited exclusive basis to develop products. The license restricts Santaris to a limited number of molecular targets that are subject to Isis' approval. Santaris has agreed to pay Isis royalties on any products developed under the license.

As part of its original license agreements with Pantheco, Isis received shares of Pantheco stock. In May 2003, Pantheco and Cureon A/S merged to form Santaris. Prior to the merger, Isis purchased additional shares of Pantheco for $55,000 as a result of anti-dilution provisions related to Pantheco's stock. After the merger and as of December 31, 2006 and 2005, Isis' ownership interest in Santaris was less than 10%. Isis' balance sheets at December 31, 2006 and 2005 included a long-term investment of $625,000, respectively, related to this equity investment, reflecting the value of Isis' initial investment and additional purchase due to anti-dilution provisions. While there is no readily determinable market value for these securities, there has been no indication that Isis' investment in Santaris has been impaired; accordingly, Isis believes that the carrying value of this investment is equal to or below its current fair market value.

Intellectual Property Licensing Agreements

In-Licensing Arrangements

Idera Pharmaceuticals, Inc., formerly Hybridon, Inc.

In May 2001, Isis entered into an agreement with Hybridon under which Isis acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. Hybridon retained the right to practice its licensed antisense patent technologies and to sublicense it to collaborators under certain circumstances. In addition, Hybridon received a non-exclusive license to Isis' suite of RNase H patents. In exchange for the license to Hybridon's antisense patents, Isis paid $15.0 million in cash and agreed to pay Hybridon $19.5 million in Isis common stock before May 2003. In return for access to Isis' patents, Hybridon agreed to pay Isis $6.0 million in Hybridon common stock before May 2004. Isis' balance sheets at December 31, 2006 and 2005 reflected a licensing asset, net of amortization, of $17.6 million and $19.5 million, respectively. During 2004 and 2005, Isis sold all of its short term investment in Hybridon for net proceeds of approximately $665,000. In September 2005, Hybridon changed its name to Idera Pharmaceuticals, Inc.

Integrated DNA Technologies, Inc.

In March 1999, Isis further solidified its intellectual property leadership position in antisense technology by licensing certain antisense patents from Integrated DNA Technologies, Inc. ("IDT"), a leading supplier of antisense inhibitors for research. The patents Isis licensed from IDT are useful in functional genomics and in making certain antisense drugs. In December 2001, Isis expanded this license agreement to allow it to exclusively sublicense this intellectual property for functional genomics purposes. Under the license, Isis paid IDT $4.9 million in license fees and will pay royalties on drugs utilizing the technology IDT licensed to Isis.

In addition, in December 2001 Isis established a long-term research-scale antisense inhibitor supply agreement with IDT. In this supply agreement IDT agreed to manufacture research-scale antisense inhibitors and research reagents to Isis' specifications. Isis paid IDT $5.0 million toward the future purchase of antisense inhibitors. During 2004, Isis recorded a non-cash charge of $4.2 million to write off the unused portion as part of its restructuring activities. (*Note 8—Restructuring Activities*).

Out-Licensing Arrangements; Royalty Sharing Agreements

Drug Royalty USA, Inc.

In December 2004, Isis sold a portion of its royalty rights in Macugen to Drug Royalty USA, Inc. ("DRC"). In exchange for this sale, DRC has paid Isis $15.0 million to date and agreed to pay Isis an additional $9.0 million in the fourth quarter of 2007. Under the terms of the agreement, Isis and DRC share the royalty rights on Macugen through 2009. After 2009, Isis retains all royalties for Macugen under its Eyetech agreement. Under the agreement, through 2009, DRC will receive the royalties on the first $500 million of annual sales of Macugen. Isis and DRC will each receive 50 percent of royalties on annual sales between $500 million and $1.0 billion. Isis retains 90 percent of all royalties on annual sales in excess of $1.0 billion and 100 percent of all royalties after 2009. Isis has retained all milestones payable to Isis by Eyetech under the license agreement.

As part of the sale, Isis agreed to pay DRC liquidated damages if any one of a defined set of defaults occurs. The amount of liquidated damages will be calculated such that DRC will receive a ten percent per

annum return, compounded quarterly on the total of all purchase price payments made by DRC to Isis through the default date minus the total of any royalties received by DRC through the default date. To date, DRC has received $5.8 million in royalties. In addition, DRC may withhold any installment of the purchase price if immediately prior to such payment, Isis fails to meet a minimum liquidity requirement equal to the then outstanding balance on its loan with Silicon Valley Bank; plus the potential amount of liquidated damages, assuming that DRC has paid the impending purchase price installment; plus its cash burn over the most recent three months. As collateral for its obligations under the sale agreement, Isis granted DRC a first priority security interest in the patents licensed by Isis to Eyetech under the license agreement and in the license agreement itself.

Eyetech Pharmaceuticals, Inc.

In December 2001, Isis licensed to Eyetech Pharmaceuticals, Inc., a wholly owned subsidiary of OSI Pharmaceuticals, Inc., certain of its patents necessary for Eyetech to develop, make and commercialize Macugen, a non-antisense drug for use in the treatment of ophthalmic diseases, that Eyetech is co-developing and commercializing with Pfizer. Eyetech paid Isis a $2.0 million upfront fee and agreed to pay Isis milestone and royalty payments in exchange for non-exclusive, worldwide rights to the intellectual property licensed from Isis.

During 2004, Isis earned $4.0 million in milestones associated with the filing of an NDA and FDA approval for Macugen for the treatment of wet age-related macular degeneration. Isis' license with Eyetech will also generate additional milestone payments aggregating up to $2.8 million for the achievement of specified regulatory milestones with respect to the use of Macugen for each additional therapeutic indication. In 2005 and 2006, Isis earned no revenue from Eyetech.

Ibis Collaborations

Isis developed, within Ibis, the Ibis T5000 Biosensor System with substantial funding from government agencies. Ibis continues to work with government collaborators to further develop the Ibis technology and applications for the Ibis T5000. Ibis is now commercializing the Ibis T5000 instrument, assay kits and its assay services to both government and non-government customers.

Commercial Agreements

Ibis plans to work with partners to manufacture, install and support Ibis T5000 instruments. For research markets Ibis is working with Bruker to accomplish this. Ibis expects in the future to work with a partner to complete development, regulatory approval, and then market the Ibis instruments for the *in vitro* diagnostics market. Ibis plans to focus on the manufacture and sale of high-volume, high-margin consumables. Ibis also generates commercial revenue through its assay services laboratory, in which it analyzes customers' samples in its own facilities, providing prospective instrument customers the opportunity to assess the Ibis T5000 Biosensor System's capabilities before purchasing an instrument.

Bruker Daltonics, Inc.

In July 2006, Ibis entered into a strategic alliance with Bruker Daltonics to manufacture and distribute the Ibis T5000 Biosensor System. Bruker Daltonics 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 Daltonics

will have exclusive rights to sell Ibis T5000 systems and Ibis assay kits for various government applications, and non-exclusive rights to sell to customers for all other applications except diagnostics. Ibis has maintained worldwide marketing rights to the diagnostics market.

Assay Services Collaboration

In July 2006, Ibis received a contract to perform forensic analyses of up to 10,000 samples in its assay services laboratory. Revenue from this contract could be up to $1.9 million. This assay services capability represents a key part of the Ibis business strategy, as it not only has the potential to be an important revenue-generating opportunity for the business, but also represents an important resource for customers evaluating the capabilities of the Ibis T5000 and collaborating in applications development.

Research and Development Collaborations

To develop the Ibis T5000 Biosensor System and its applications, Ibis received contracts and grants from a number of government agencies, including Defense Advanced Research Projects Agency ("DARPA"), the Department of Homeland Security ("DHS"), the Centers for Disease Control ("CDC"), and the National Institute of Allergy and Infectious Diseases ("NIAID"). Government collaborations continue to represent a significant source of funding for the Ibis T5000 program. As a result of these collaborations, Ibis is now developing various applications for the Ibis T5000 Biosensor System that it will sell to commercial customers, including government collaborators.

Biodefense

The earliest application of the Ibis T5000 Biosensor System to be funded by the government focused on bioagent detection. In March 2004, Ibis received a two-year contract from DARPA under a subcontract from Science Applications International Corporation ("SAIC") to further develop the Ibis biosensor system to identify infectious agents in biological warfare attacks. As part of this program, Ibis successfully demonstrated proof-of-principle of the Ibis biosensor system by identifying a variety of bacteria and viruses in both environmental and human clinical samples. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis delivered its first Ibis biosensor system to the United States Army Medical Research Institute of Infectious Diseases ("USAMRIID") for use in biodefense.

Forensics

Microbial forensics is a type of forensics used to investigate crimes involving infectious organisms. Microbial forensics uses the "biological fingerprint" of an infectious organism to help pinpoint the source, allowing law enforcement and public health officials to effectively respond to a biological threat. Additionally, through a government grant, Ibis is continuing its ongoing development of an informational database on microbial agents. The program is a database of biological threat agents, their DNA sequences, and their effects, that law enforcement officials can use to confer deterrence and support forensic investigations. In 2005, under a subcontract from SAIC and with support from DARPA, Ibis installed its second biosensor system to the DHS's National Bioforensic Analysis Center ("NBFAC")for use in bioforensics.

Epidemiological Surveillance, Infectious Disease Research and Hospital-Associated Infection Control

Ibis and its government partners continue to develop applications for the T5000 Biosensor System to rapidly identify, monitor, and control infectious diseases. Specifically, in August 2005, Ibis received a three-year grant worth up to $4.9 million from the NIAID. The grant funds the continued development of applications to diagnose infectious diseases and to identify and control hospital-associated infections ("HAI") using the Ibis T5000 Biosensor System. In September 2006, Ibis successfully completed the first phase of this grant and has been granted funding for the second and third phases of the grant, which includes installing an Ibis T5000 Biosensor System at Johns Hopkins University Medical Center. The purpose of the grant is to develop and validate a broad range of respiratory and blood-borne infectious agents, including bacteria and viruses on the NIAID priority list. In addition to deployment of an Ibis T5000, the second and third phases of the grant—approximately $2.6 million—include funding for the purchase of assay kits to analyze human samples in validation studies.

In addition, in September 2003, Ibis received a three-year grant for up to $6.0 million from the CDC to develop and apply the Ibis biosensor system technology to the surveillance of human infectious disease in the United States. Ibis installed an Ibis biosensor system at the CDC in September 2006 under this contract. Earlier in 2006, Ibis installed a biosensor system at the Naval Health Research Center. The Navy is using the Ibis biosensor system in respiratory disease surveillance and has analyzed hundreds of samples on the Ibis biosensor system at its facility.

7. Segment Information and Concentration of Business Risk

Segment Information

Isis reports its financial results in two reportable segments, Drug Discovery and Development, and its Ibis Biosciences, Inc. subsidiary. Segment loss from operations includes research and development, selling, general and administrative expenses, and other charges attributable to the segment. Costs excluded from the segments consist of restructuring activities and prior to 2006, compensation benefit related to the variable accounting for stock options.

The Drug Discovery and Development segment generates revenue from collaborations with corporate partners and from licensing proprietary patent rights. Revenue from collaborations with corporate partners may consist of upfront payments, funding for research and development activities, milestones and royalties. This segment's proprietary technology to discover and characterize novel antisense inhibitors has enabled its scientists to modify the properties of its antisense drugs for optimal use with particular targets and thus, to produce a broad proprietary portfolio of drugs applicable to many disease targets.

The Ibis Biosciences segment generates revenue from grants and contracts from United States government agencies, from sales of its Ibis T5000 Biosensor System and related assay kits and the analysis of samples within Ibis' assay services laboratory.

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.

The following is information for revenue and loss from operations by segment for the years ended December 31, 2006 and 2005.

December 31, 2006	Drug Discovery and Development	Ibis	Corporate	Total
Revenue:				
Research and development	$ 5,418	$ 9,117	$ —	$ 14,535
Commercial revenue(1)	—	556	—	556
Licensing and royalty	9,441	—	—	9,441
Total segment revenue	$ 14,859	$ 9,673	$ —	$ 24,532
Loss from operations	$(61,714)	$(6,940)	$536	$(68,118)

December 31, 2005	Drug Discovery and Development	Ibis	Corporate	Total
Revenue:				
Research and development	$ 16,817	$11,793	$ —	$ 28,610
Licensing and royalty	11,523	—	—	11,523
Total segment revenue	$ 28,340	$11,793	$ —	$ 40,133
Loss from operations	$(48,537)	$ (2,229)	$(6,416)	$(57,182)

December 31, 2004	Drug Discovery and Development	Ibis	Corporate	Total
Revenue:				
Research and development	$ 21,684	$10,933	$ —	$ 32,617
Licensing and royalty	10,007	—	—	10,007
Total segment revenue	$ 31,691	$10,933	$ —	$ 42,624
Loss from operations	$(82,135)	$ (3,297)	$(32,421)	$(117,853)

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

Concentrations of Business Risk

Isis has historically funded its operations in part from collaborations with corporate partners and as it relates to Ibis Biosciences, from collaborations with various government agencies. Beginning in the second half of 2006, Ibis Biosciences began selling commercial products and services. 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:

	2006	2005	2004
Partner A	33%	17%	0%
Partner B	14%	9%	6%
Partner C	12%	4%	2%
Partner D	8%	14%	18%
Partner E	5%	27%	37%
Partner F	3%	9%	13%

During 2006, 2005, and 2004, Isis derived approximately 37%, 30%, and 28%, respectively, of its revenue from agencies of the United States Government. In 2006, two significant customers accounted for 14% and 12% of revenue from agencies of the United States Government and in 2005 and 2004, one significant customer accounted for 14% and 18%, respectively.

Contract receivables from four significant partners comprised approximately 25%, 20%, 19% and 16% of contract receivables at December 31, 2006. Contract receivables from four significant partners comprised approximately 39%, 13%, 12% and 12% of contract receivables at December 31, 2005.

8. Restructuring Activities

For the year ended December 31, 2004, Isis recorded $32.4 million in costs associated with its restructuring activities resulting from its strategic decision to focus its resources on key programs. The 2004 charge for restructuring activities consisted of non-cash write-downs of tangible and intangible assets that Isis considered to be non-essential to its new focus, including excess or idle equipment, inventories, patent costs, and certain prepaid expenses.

For the year ended December 31, 2005, Isis recorded $7.0 million in costs associated with its restructuring activities. The 2005 charge for restructuring activities consisted of costs associated with 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 connection with the consolidation of its U.S. facilities, Isis completed the sale of the three buildings that it owned for a net gain of $1.5 million.

For the year ended December 31, 2006, Isis recorded a benefit of $536,000 associated with its restructuring activities. In 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. Additionally, 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. These benefits were included in the restructuring activities for the year ended December 31, 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.

	Facility Consolidation and Closure Related Costs	Employee Separation Costs	Contract Termination Costs	Other Costs	Total
Balance at December 31, 2004.	$ —	$ —	$ —	$ —	$ —
Accrued and expensed.....	1,709	3,751	910	590	6,960
Charged against accrual	(853)	(3,751)	(145)	(464)	(5,213)
Balance at December 31, 2005.	856	—	765	126	1,747
Accrued and expensed.....	(282)	—	(265)	11	(536)
Charged against accrual	(574)	—	(500)	(137)	(1,211)
Balance at December 31, 2006.	$ —	$ —	$ —	$ —	$ —

9. Employee Post Employment Benefits

Isis has an employee 401(k) salary deferral plan, covering all domestic employees. Employees may make contributions by withholding a percentage of their salary up to the IRS annual limit ($15,000 and $20,000 in 2006 for employees under 50 years old and over 50 years old, respectively). Isis made approximately $362,000, $404,000 and $478,000 in matching contributions for the years ended December 31, 2006, 2005 and 2004, respectively.

10. Affiliate Supplementary Disclosure

Orasense and Hepasense

In April 1999 and January 2000, Isis and Elan formed Orasense, Ltd. and Hepasense, Ltd., respectively, both Bermuda limited companies. Each joint venture was owned 80.1% by Isis and 19.9% by Elan. In 2002, Elan concluded its participation in both the Orasense and Hepasense collaborations. Additionally, Isis regained all rights to ISIS 104838, the compound that Elan and Isis were developing within Orasense. In June 2004, Isis acquired Elan's minority interest in Orasense and Hepasense and eliminated all future royalties to Elan related to the technology for the formulation of oral drugs developed within the Orasense collaboration. As a result, Isis owned 100% of Orasense and Hepasense at December 31, 2004. Isis dissolved the Hepasense and Orasense subsidiaries in July 2005 and October 2006, respectively. In 2004, Orasense incurred approximately $811,000 in research and development expenses through the date of Isis' acquisition of Elan's minority interest in Orasense.

11. 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 Isis with the American Arbitration Association in San Diego, California. The Demand related to a February 17, 1994 license agreement between Ajinomoto and Isis, that purports to license 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 Isis 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 recorded a $418,000 charge, which represents the present value of Isis' liability under this agreement.

Annual payments of $60,000 will be made until year 2035. (*Note 3—Long-Term Obligations and Commitments*).

12. Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2006, and 2005 are as follows (in thousands, except per share data).

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2006 Quarters				
Revenue	$ 4,958	$ 4,375	$ 3,253	$ 11,946
Operating expenses(1)	20,974	21,477	21,517	28,682
Loss from operations(1)	(16,016)	(17,102)	(18,264)	(16,736)
Net loss applicable to common stock(1)	$(17,480)	$ (2,172)	$(12,105)	$(14,146)
Basic and diluted net loss per share(3)	$ (0.24)	$ (0.03)	$ (0.16)	$ (0.18)

	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
2005 Quarters				
Revenue	$ 7,442	$ 10,592	$ 7,458	$14,641
Operating expenses(2)	30,949	23,515	19,602	23,249
Loss from operations(2)	(23,507)	(12,923)	(12,144)	(8,608)
Net loss applicable to common stock(2)	$(29,658)	$(19,659)	$(15,172)	$ (7,912)
Basic and diluted net loss per share(3)	$ (0.52)	$ (0.34)	$ (0.24)	$ (0.11)

(1) Includes benefits related to restructuring activities of $0.5 million incurred during the year ended December 31, 2006.

(2) Includes charges related to restructuring activities of $7.0 million incurred during the year ended December 31, 2005.

(3) Net loss per share is computed independently for each of the quarters presented. Therefore, the sum of the quarterly net loss per share will not necessarily equal the total for the year.

Exhibit 21.1

LIST OF SUBSIDIARIES FOR THE REGISTRANT

Ibis Biosciences, Inc., a Delaware Corporation

Isis Pharmaceuticals Singapore Pte Ltd., a Singapore Limited Private Company

Isis USA Limited, a United Kingdom Limited Private Company

PerIsis I Development Corporation, a Delaware Corporation

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements (Form S-3 Nos. 33-55790, 33-72124, 33-75068, 33-96138, 333-71911, 333-90811, 333-38844, 333-71116, 333-71176, 333-89066, 333-89626, 333-128156, 333-130639, 333-134380 and Form S-8 Nos. 33-42356, 33-42970, 33-51236, 33-54840, 33-58450, 33-75150, 33-90780, 333-05825, 333-55683, 333-40336, 333-59296, 333-91572, 333-106859, 333-116962, 333-125911, 333-133853) of Isis Pharmaceuticals, Inc. and in the related Prospectuses of our reports dated March 6, 2007, with respect to the consolidated financial statements of Isis Pharmaceuticals, Inc., Isis Pharmaceuticals, Inc.'s management's assessment of the effectiveness of internal control over financial reporting, and the effectiveness of internal control over financial reporting of Isis Pharmaceuticals, Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2006.

/s/ ERNST & YOUNG LLP

San Diego, California
March 14, 2007

Exhibit 31.1

CERTIFICATION

I, Stanley T. Crooke, certify that:

1. I have reviewed this Annual Report on Form 10-K of Isis Pharmaceuticals, Inc.;
2. Based on my knowledge, this annual 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 annual report;
3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual 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 annual 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: March 14, 2007

/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 Annual Report on Form 10-K of Isis Pharmaceuticals, Inc.;
2. Based on my knowledge, this annual 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 annual report;
3. Based on my knowledge, the consolidated financial statements, and other financial information included in this annual 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 annual 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: March 14, 2007

/s/ B. LYNNE PARSHALL

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

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), 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 Annual Report on Form 10-K for the period ended December 31, 2006, to which this Certification is attached as Exhibit 32.1 (the "Annual 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 Annual Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Annual Report and the results of operations of the Company for the period covered by the Annual Report.

Dated: March 14, 2007

/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.

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Isis Pharmaceuticals, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

Board of Directors

Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board and Chief Executive Officer
Isis Pharmaceuticals, Inc.

Spencer R. Berthelsen, M.D.
Chairman, Board of Directors and Managing Director
Kelsey-Seybold Clinic

Richard D. DiMarchi, Ph.D.
Professor and Chair of the Chemistry Department
Indiana University

Joseph Klein, III
Managing Director
Gauss Capital Advisors, LLC

Frederick T. Muto, J.D.
Partner
Cooley Godward Kronish LLP

B. Lynne Parshall, J.D.
Executive Vice President, Chief Financial Officer and Secretary
Isis Pharmaceuticals, Inc.

John C. Reed, M.D., Ph.D.
President and Chief Executive Officer
Burnham Institute for Medical Research

Joseph H. Wender
Senior Managing Director
GSC Group

Management

Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board and Chief Executive Officer

B. Lynne Parshall, J.D.
Executive Vice President, Chief Financial Officer and Secretary

Jeffrey M. Jonas, M.D.
Executive Vice President

C. Frank Bennett, Ph.D.
Senior Vice President, Research

David J. Ecker, Ph.D.
Vice President of Isis and Chief Scientific Officer of Ibis Biosciences, Inc., a wholly owned subsidiary of Isis Pharmaceuticals, Inc.

Arthur A. Levin, Ph.D.
Senior Vice President, Development

Michael J. Treble
Vice President of Isis and President of Ibis Biosciences, Inc., a wholly owned subsidiary of Isis Pharmaceuticals, Inc.

Mark K. Wedel, M.D., J.D.
Senior Vice President, Development and Chief Medical Officer

Transfer Agent

American Stock Transfer & Trust Company
59 Maiden Lane
New York, NY 10038

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4401 Eastgate Mall
San Diego, CA 92121

Outside Patent Counsel

Woodcook Washburn LLP
One Liberty Place, 46th Floor
Philadelphia, PA 19103

Independent Registered Public Accounting Firm

Ernst & Young LLP
4370 La Jolla Village Drive, Suite 500
San Diego, CA 92122

Common Stock Symbol

NASDAQ: ISIS

Corporate

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
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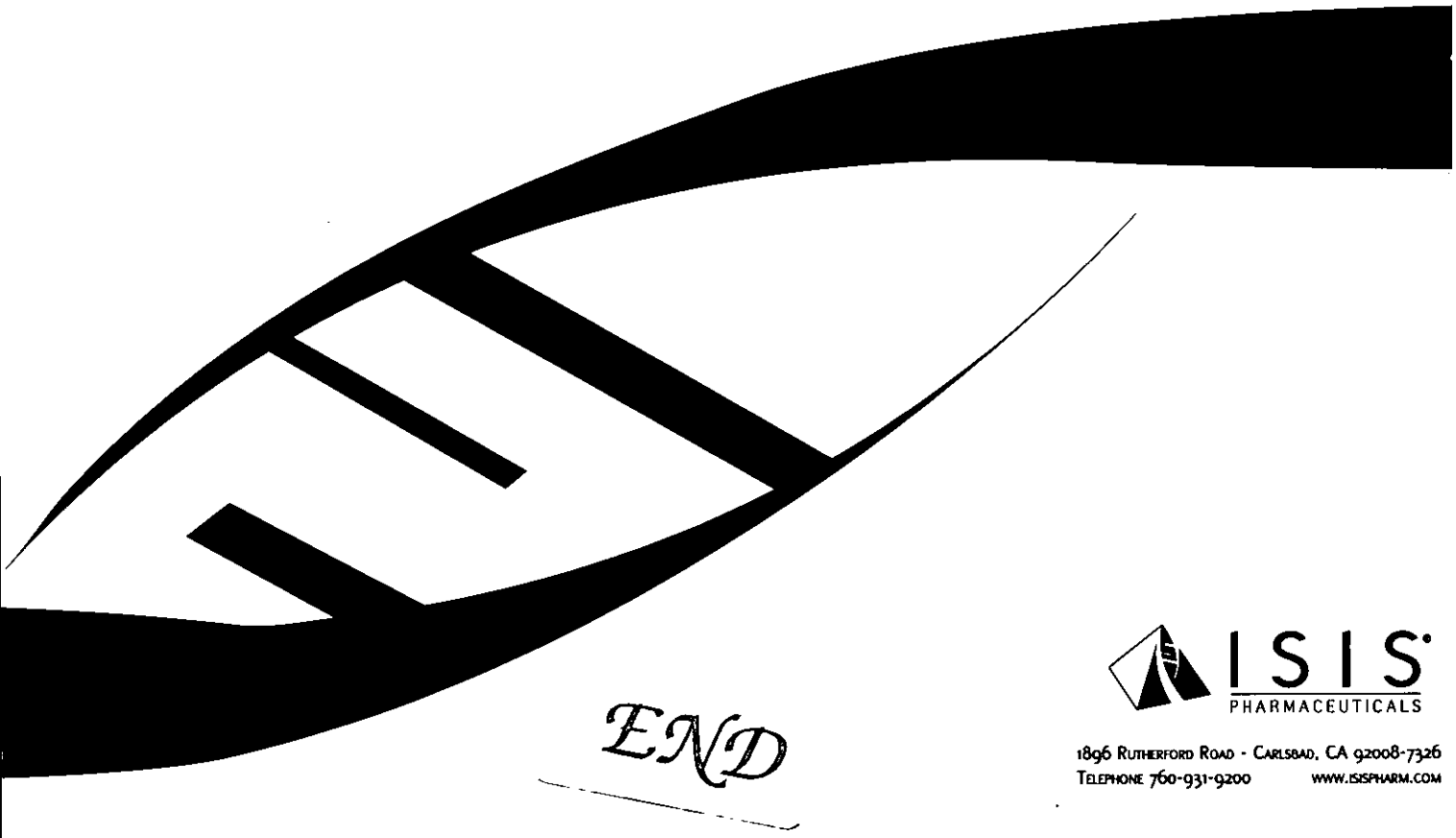
Website www.isispharm.com
E-mail info@isisph.com



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