==========

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, 1997
COMMISSION FILE NUMBER 0-19125

ISIS PHARMACEUTICALS, INC.
(EXACT NAME OF REGISTRANT AS SPECIFIED IN ITS CHARTER)

DELAWARE	33-0336973
(STATE OR OTHER JURISDICTION OF INCORPORATION OR ORGANIZATION)	(IRS EMPLOYER IDENTIFICATION NO.)

2292 FARADAY AVE., CARLSBAD, CA 92008
(ADDRESS OF PRINCIPAL EXECUTIVE OFFICES, INCLUDING ZIP CODE)

760-931-9200
(REGISTRANT'S TELEPHONE NUMBER, INCLUDING AREA CODE)

SECURITIES REGISTERED PURSUANT TO SECTION 12(B) OF THE ACT:

NONE

SECURITIES REGISTERED PURSUANT TO SECTION 12(G) OF THE ACT:

COMMON STOCK, $.001 PAR VALUE

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

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. Yes [X] No [ ].

The approximate aggregate market value of the common stock held by non-affiliates of the Registrant, based upon the last sale price of the common stock reported on the National Association of Securities Dealers Automated Quotation National Market System was $326,796,000 as of February 27, 1998.*

The number of shares of common stock outstanding as of February 27, 1998 was 26,760,742.

DOCUMENTS INCORPORATED BY REFERENCE
(TO THE EXTENT INDICATED HEREIN)

Registrant's definitive Proxy Statement which will be filed on or before April 13, 1998 with the Securities and Exchange Commission in connection with Registrant's annual meeting of stockholders to be held on May 22, 1998 is incorporated by reference into Part III of this Report.

- ---

* Excludes 2,441,014 shares of common stock held by directors and officers and stockholders whose beneficial ownership exceeds 10 percent of the shares outstanding at February 27, 1998. 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.

==========

THIS FORM 10-K CONTAINS FORWARD-LOOKING STATEMENTS REGARDING THE COMPANY'S BUSINESS, THE THERAPEUTIC AND COMMERCIAL POTENTIAL OF ANTISENSE AND COMBINATORIAL TECHNOLOGY AND ISIS' PRODUCTS IN DEVELOPMENT. 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 AND THE ENDEAVOR OF BUILDING A BUSINESS AROUND SUCH POTENTIAL PRODUCTS. ACTUAL RESULTS COULD DIFFER MATERIALLY FROM THOSE DISCUSSED IN THIS FORM 10-K. FACTORS THAT COULD CAUSE OR CONTRIBUTE TO SUCH DIFFERENCES INCLUDE, BUT ARE NOT LIMITED TO, THOSE DISCUSSED IN THIS FORM 10-K INCLUDING THOSE IDENTIFIED IN THE SECTION OF ITEM 1 ENTITLED "RISK FACTORS." AS A RESULT, THE READER IS CAUTIONED NOT TO RELY ON THESE FORWARD-LOOKING STATEMENTS.

PART I

ITEM 1. BUSINESS

OVERVIEW

Isis Pharmaceuticals, Inc. ("Isis", the "Company" or "we") is a leader in the discovery and development of a new class of drugs based on antisense technology. With antisense technology, we believe we can design drugs that are safer and more effective than traditional drugs. Isis combines its expertise in molecular and cellular biology with antisense drug discovery techniques to design drugs to fight a wide range of diseases, including infectious and inflammatory diseases and cancer. Today, we have 6 antisense compounds in human clinical trials, with additional compounds arising out of our broad research program in preclinical development.

Through Isis' expertise in medicinal chemistry and RNA structure and function, we have also developed a proprietary RNA-targeting drug discovery program. This program allows us to use genomic information to identify novel structural targets and to quickly create and screen, as potential drugs, large libraries of small molecule compounds designed to inhibit those targets.

This chart represents the "pipeline" of Isis products currently in preclinical and clinical development:

ISIS DEVELOPMENT PIPELINE

	PRECLINICAL	IND CANDIDATE	PHASE I	PHASE II	PHASE III
FOMIVIRSEN (ISIS 2922)					
CMV Retinitis					
ISIS 2302					
Crohn's Disease					
Psoriasis					
Rheumatoid Arthritis					
Ulcerative Colitis					
Kidney Transplant Rejection					
ISIS 3521					
Cancer					
ISIS 5132					
Cancer					
ISIS 5320					
HIV					
ISIS 2503					
Cancer					
ISIS 13312					
CMV Retinitis					

We have completed Phase III clinical trials of FOMIVIRSEN (ISIS 2922) to treat CMV retinitis in AIDS patients. In one Phase III trial, fomivirsen has demonstrated statistical significance (p=0.0001) in delaying disease

progression and was well tolerated by patients, producing no serious side effects. These data are from 1 of 4 trials that comprise the Phase III clinical development program for fomivirsen. Analysis of the other Phase III studies is currently being completed. We plan to file both a New Drug Application ("NDA") with the U.S. Food and Drug Administration ("FDA") and a corresponding European application in early 1998. In July 1997, we entered into an agreement with CIBA Vision Corporation ("CIBA Vision") granting CIBA Vision exclusive worldwide distribution rights for fomivirsen.

ISIS 2302 is in Phase II clinical trials to treat inflammatory diseases and conditions. ISIS 2302 targets intercellular adhesion molecule-1 ("ICAM-1"), which is involved in many such diseases. With our partner, Boehringer Ingelheim International GmbH ("Boehringer Ingelheim"), we are testing ISIS 2302 against Crohn's disease, psoriasis, rheumatoid arthritis, ulcerative colitis and renal transplant rejection. In a Phase II study of patients with Crohn's disease, an encouraging number of patients receiving ISIS 2302 had their symptoms improve. A statistically significant ($p=0.0001$) number were also able to reduce (and, for some patients, completely eliminate) their steroid use (the most common treatment for Crohn's disease). Because of these positive results, we began a pivotal quality trial of ISIS 2302 in Crohn's disease in the second quarter of 1997. With respect to the other phase II trials, we are in the follow-up period for the rheumatoid arthritis study. We have also decided that, based on the results of the psoriasis study, we will study use of ISIS 2302 in a topical skin application. The ulcerative colitis and kidney transplant studies are on-going.

ISIS 3521 is in Phase II clinical trials as an anticancer agent, both alone and in combination with traditional cancer chemotherapies. On-going studies are exploring the effect of this drug in treating a variety of cancer tumors. This compound targets protein kinase C ("PKC")-[Greek alpha], a protein associated with abnormal cell growth. We are developing ISIS 3521 as part of our collaboration with Novartis Pharma AG ("Novartis"). In Phase I trials, ISIS 3521 stabilized disease, reduced tumor mass and reduced tumor markers in a number of patients with ovarian cancer, lymphoma and lung cancer. In those trials, ISIS 3521 caused no significant side effects.

ISIS 5132 is in Phase II clinical trials as an anticancer agent, both alone and in combination with traditional cancer chemotherapies. The Phase II trials are studying the effect of this drug in treating a variety of cancer tumors. This compound inhibits expression of C-raf kinase, another type of protein associated with abnormal cell growth. We are also developing ISIS 5132 as part of our collaboration with Novartis. In Phase I clinical trials of ISIS 5132, the compound showed evidence of antitumor activity in patients with ovarian, renal, pancreatic, and colon cancers. This compound was also well tolerated by patients in the Phase I studies.

ISIS 2503 is in Phase I clinical trials as an anticancer agent. This compound inhibits expression of Ha-ras, yet another protein associated with cancer. The Phase I trial is being conducted in patients with a variety of solid tumors that have not responded to standard cancer therapies.

ISIS 13312 is in Phase I clinical trials to treat CMV retinitis in AIDS patients. ISIS 13312 is based on novel, improved antisense chemistry. In preclinical studies, ISIS 13312 appears to be safer and more stable than fomivirsen, potentially allowing less frequent dosing than fomivirsen. CIBA Vision has an option to exclusively market and distribute ISIS 13312 worldwide.

Isis also has several antisense compounds in preclinical development, most of which incorporate novel chemical classes that may provide improved potency, reduced side effects, less frequent dosing and the possibility of oral delivery. These include improved antisense inhibitors of ICAM-1 and related cell adhesion molecules VCAM-1 and PECAM-1, C-raf kinase and 2 isotypes of the PKC family, including PKC-[Greek epsilon]. A compound inhibiting proteins critical for Hepatitis C ("HCV") gene expression is also in preclinical development.

We have many research programs that use both antisense and RNA-targeting drug discovery technologies to identify compounds that inhibit

targets associated with other diseases. Our antisense research programs focus on targets associated with infectious, inflammatory and cardiovascular diseases and cancer. They combine our expertise in molecular biology and drug discovery with antisense tools to enable rapid identification of potent inhibitors of disease causing proteins. We are then able to apply our medicinal chemistry expertise to specifically tailor a compound to the particular disease indication targeted. Our medicinal chemistry programs have developed novel chemistries that allow us to design new antisense compounds that are potentially safer and more active than current antisense drugs and which have the potential to allow more convenient forms of dosing including oral delivery. Our RNA-

targeting program is focused on identifying the structural elements of RNA targets which are important in initiating or maintaining diseases, and designing compounds that interfere with the function of these RNA targets, including those involved in viral and bacterial infections. This program is also focused on designing small molecules to block the production or function of cell adhesion molecules.

We have successfully leveraged our technology through supportive corporate collaborations with Novartis, Boehringer Ingelheim and CIBA Vision. These collaborations increase our financial resources, improve our technological strength and establish valuable development and commercial relationships. As a result, we have been able, and expect to continue, to pursue drug discovery and development activities aggressively. We have retained substantial commercial participation in all of our drug candidates, including those funded by corporate collaborators.

Isis has focused significant efforts on developing cost-effective, large-scale, Good Manufacturing Practices ("GMP") manufacturing capability for antisense compounds. We currently manufacture antisense compounds to meet all of our research and clinical needs, as well as the needs of our partners. We have achieved significant manufacturing cost reductions through chemistry and process improvements. We believe that, with reasonably anticipated benefits resulting from increases in scale, we will be able to manufacture antisense compounds at commercially attractive prices. We are actively preparing for a manufacturing pre-approval inspection by the FDA which will follow the filing of our first NDA. Under the terms of our agreement with CIBA Vision, Isis will manufacture all of the commercial supplies of fomivirsen.

ISIS DRUG DISCOVERY AND DEVELOPMENT

The goal of drug discovery is to create chemical compounds that can help fight or prevent disease. Isis' antisense and RNA-targeting drug discovery programs were founded on the Company's expertise in medicinal chemistry, RNA biochemistry and molecular and cellular biology. We have assembled a team of scientists skilled in these core disciplines to apply the technology to both of our drug discovery platforms. Once a drug is designed, our significant expertise in medicinal chemistry enables us to specifically tailor the chemical structure of the lead compound for its intended use.

ANTISENSE DRUG DISCOVERY

Almost all human diseases are a result of inappropriate protein production or performance. Traditional drugs are designed to interact with the proteins in the body that are supporting or causing a disease. Antisense technology is different than traditional drug development because it targets disease-causing proteins before they are produced. Antisense drugs can be designed to treat a wide range of diseases, including infectious, inflammatory and cardiovascular diseases, and cancer.

Antisense technology represents a new model for drug discovery because it focuses on compounds that interact with messenger RNA ("mRNA"), which has not been a site for traditional drug interaction. Using the information contained in mRNA, Isis designs chemical structures, easily recognized by the

body, which resemble mRNA and DNA. These potent "antisense" oligonucleotides inhibit the production of disease-causing proteins. This method of drug design is highly productive and has allowed Isis in 9 years to create a substantial pipeline of drug candidates, including 6 compounds currently in clinical trials.

Design of antisense compounds is less complex, more rapid and more efficient than traditional drug design directed at protein targets. Traditional drug design usually begins by characterizing the three-dimensional structure of the protein target in order to design a prototype drug to interact with it. Proteins are complex molecules with structures that are difficult to predict. Antisense compounds, on the other hand, are designed to bind to mRNA structures, which are more easily understood and predicted. Prototype antisense drugs can be designed as soon as the sequence for the mRNA receptor is identified.

6

Isis' early research efforts focused on answering basic questions regarding antisense-based therapeutics, including their stability, their ability to be taken up by the target cells, their efficacy and the cost of manufacturing them. In the 9 years since its founding, Isis has made significant progress in understanding and using antisense technology to create drugs, and has established a leadership position in this field.

THE MECHANISM OF ANTISENSE DRUGS

Genes carry the information that cells need to produce proteins. Specific genes contain information to produce specific proteins at the genetic level. The human genome and its collection of more than 100,000 genes contains the information required for the human body to produce all proteins. Genes are made up of DNA, a molecule that contains the information about when and how much of which protein to produce, depending on what function is to be performed. The DNA molecule is a "double helix" -- a duplex of entwined strands. In each strand, the building blocks of DNA, the nucleotides, are bound or "paired" with complementary nucleotides on the other strand. The precise sequence of a nucleotide chain, called the "sense" sequence, is a blueprint for the information that is used during protein production. The sequence of a nucleotide chain that is precisely complementary to a given sense sequence is called its "antisense" sequence.

In the cell nucleus, the information in the gene necessary for the production of a protein is copied from 1 strand of DNA into precursor mRNA through a process called transcription. After processing into mature mRNA, the mRNA moves from the nucleus of the cell into the cell cytoplasm, which contains amino acids. The information encoded in a single mRNA is then translated into many copies of the sequence of amino acids that builds the protein.

Antisense drugs are mirror or complementary images of small segments of mRNA. To create antisense drugs, nucleotides are linked together in short chains called oligonucleotides. Each antisense drug is designed to bind to a specific sequence of nucleotides in its mRNA target to inhibit production of the protein encoded by the target mRNA. By preventing the production of the disease-causing protein, and acting in the early stage of the disease-causing process, antisense drugs have the potential to provide greater therapeutic benefit than traditional drugs, which do not act until after the disease causing protein has been produced.

Antisense drugs can be designed to be much more selective than traditional drugs. Because antisense drugs interact by binding to mRNA and not, as traditional drugs do, by binding to proteins, antisense drugs are able to selectively inhibit 1 protein among a closely related group of proteins without having an impact on the other members of the group. This property allows Isis to 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. As a result of this unique selectivity, antisense drugs have the potential to be far less toxic than traditional drugs because they can be designed to minimize the impact on unintended targets.

RNA-TARGETING DRUG DISCOVERY

The prime objective of Isis' small molecule RNA targeting program is to identify novel compounds that kill drug-resistant bacteria and are not toxic to humans. Targeting RNA structures in bacteria is a novel approach to drug discovery. This drug development strategy, when perfected, will likely have application across a wide spectrum of non-infectious human diseases.

Three-dimensional shapes provide the opportunity to target RNA. Recent advances in molecular biology have revealed that RNA structures are surprisingly complex. In contrast to the regular helical nature of DNA, RNA strands fold back on themselves to produce unique three- dimensional shapes that rival proteins in their complexity. The specific proteins that bind to RNA recognize these shapes. The amino acid side chains from these proteins fit into "pockets" formed in the folded RNA to form specific contacts. These pockets are ideal receptor sites for small molecules. Evidence that small molecules can

specifically bind to structured RNA already exists. Some of the most powerful, naturally occurring antibiotics work by binding to structured RNA.

With recently acquired knowledge of RNA structures and new sequence data from the gene sequence ("genomic") databases, Isis is developing a new drug discovery paradigm: Specific targeting of RNA with small drug-like molecules. New software is being used to identify particular RNA structures that we can target. New molecular modeling techniques can be used to predict the shape of drug binding pockets in RNA structures. With a working approximation of the shape of a target, Isis is designing libraries of drug-like molecules that can bind to the RNA targets. We will use mass spectrometry to facilitate screening large numbers of small molecules against multiple RNA targets simultaneously.

PRODUCTS UNDER DEVELOPMENT

Isis' drug discovery programs use antisense and combinatorial drug discovery technologies to identify compounds to treat infectious and inflammatory diseases and cancer. The following table outlines each product under development, its target, disease indication and development status, as well as Isis' commercial rights.

ISIS PRODUCTS IN DEVELOPMENT

CLINICAL DEVELOPMENT

COMPOUND	TARGET	DISEASE INDICATION	DEVELOPMENT STATUS	COMMERCIAL RIGHTS
Fomivirsen (ISIS 2922)	CMV	Retinitis	Completed Phase III NDA filing pending	Isis/CIBA Vision (1)
ISIS 2302	ICAM-1	Crohn's disease Psoriasis Rheumatoid arthritis Ulcerative colitis Kidney transplant rejection	Pivotal trial Phase II Phase II Phase II Phase II	Isis/ Boehringer Ingelheim (2)
ISIS 3521	PKC-[Greek alpha]	Cancer	Phase II	Novartis (3)
ISIS 5132	C-raf kinase	Cancer	Phase II	Novartis (3)
ISIS 2503	Ha-ras	Cancer	Phase I	Isis
ISIS 13312	CMV	Retinitis	Phase I	Isis/CIBA Vision (1)

(1) CIBA Vision has the exclusive right to distribute fomivirsen. CIBA

Vision also has an option to acquire the exclusive license to market and distribute ISIS 13312.

(2) Isis and Boehringer Ingelheim are co-developing ISIS 2302 and may develop other cell adhesion compounds. The companies will split the profits equally if ISIS 2302 is commercialized.

(3) Isis is developing ISIS 3521 and ISIS 5132 under the direction of Novartis and at Novartis' expense, and may co-develop 2nd generation compounds as well.

Isis also has a significant research program with the potential to yield additional development candidates in the future. As described in the section of this report entitled "Risk Factors - Uncertainties Associated with Clinical Trials," the product candidates listed in the preceding table may not progress beyond their current status or yield a commercially viable product.

CYTOMEGALOVIRUS (CMV)RETINITIS

Individuals with suppressed immune systems, such as those with AIDS resulting from the HIV virus, are susceptible to opportunistic infections caused by CMV. In the AIDS population, retinitis caused by CMV is the primary cause of blindness. There are more than 250,000 active AIDS cases in the United States. The introduction of new anti-HIV drugs, particularly protease inhibitors and combination treatment regimens, have prolonged survival in HIV-infected individuals. Over the last 2 years this has resulted in a decline in mortality from AIDS, accompanied by a decline in the incidence of many opportunistic infections including CMV. Nevertheless, because of side effects and poor compliance with HAART, many of the approximately 1 million HIV infected individuals will probably ultimately progress to and through the advanced stages of AIDS. A significant percentage of these AIDS patients may develop CMV retinitis (CMV retinitis generally occurs in the advanced stages of AIDS).

The drugs that are available now for CMV retinitis have limitations, including the creation of viral resistance. Currently approved drugs for CMV retinitis are ganciclovir, foscarnet and cidofovir. Foscarnet and cidofovir are available in intravenous (IV) dosing forms only. Ganciclovir is available in IV and oral doses, as well as in an intraocular implant form. In order to begin and maintain IV treatment with ganciclovir and foscarnet, patients require daily administrations of the drug through lines that are placed permanently in the veins to allow easy access to the blood stream. Each drug is associated with significant toxic effects to the body. Oral ganciclovir is approved for preventive treatment and maintenance therapy, but is less effective than IV ganciclovir and still carries significant side effects. The ganciclovir intraocular implant is a small disk that is surgically implanted in the patient's eye, and provides local sustained release of the drug for up to 8 months. However, this treatment is associated with impaired vision for 2 to 4 weeks after implantation in most patients, and the implant itself has also been associated with an increased incidence of retinal detachment that can result in permanent blindness. There is a 12-18% chance of retinal detachment after the first implant and a near 30% chance following a second or third implant. Cidofovir is administered intravenously less frequently than ganciclovir or foscarnet: weekly for the initial therapy and every 2 weeks for maintenance therapy. Cidofovir is also associated with significant toxicities, particularly to the kidney. For that reason, the patient must take other drugs and follow strict safety measures over a period of approximately 12 hours to manage toxicities.

FOMIVIRSEN. Fomivirsen is an antisense compound discovered by Isis for the treatment of CMV retinitis. Fomivirsen is given by injection into the eye and is well tolerated by patients.

The Phase III program for fomivirsen includes 4 randomized controlled studies. The first study compares immediate fomivirsen therapy with no therapy until disease progression; the second compares fomivirsen treatment in combination with ganciclovir to ganciclovir treatment alone; and the third and

fourth trials study different dosing regimens for fomivirsen in a patient population with advanced, resistant CMV retinitis. All 4 study designs examine the time to disease progression. The trials are being conducted in North America, Europe, South America and Australia.

In the first of 4 Phase III studies, fomivirsen delayed disease progression (statistical significance of p=0.0001) and was well-tolerated, producing no serious side effects. In this trial, treatment of patients with newly-diagnosed, previously untreated CMV retinitis with fomivirsen was compared to deferred treatment. The intent to treat analysis (all patients enrolled in the trial) demonstrated that the median time to disease progression for the immediate treatment group was 71 days versus 13 days for the deferred treatment group (p=0.0001). Fomivirsen administered by intravitreal injection was well-tolerated by patients. No patients were discontinued from this study because of fomivirsen-related ocular side effects. A large number of patients receiving immediate treatment with fomivirsen remained on study for prolonged periods of several months or more.

The Phase III trials of fomivirsen were completed at the end of 1997. Analysis of the other Phase III studies is currently being completed. We anticipate filing both an NDA and a corresponding European regulatory application in early 1998.

As CMV retinitis patients are living longer with their disease due to improvements in the management of HIV infection and AIDS, there is increasing need for more CMV retinitis treatment options, particularly ones with novel mechanisms of action such as fomivirsen. Local therapy with fomivirsen could provide therapeutic benefit without significant side effects or the need for intravenous treatments, reserving treatment with oral ganciclovir or other systemic CMV therapies in combination with fomivirsen for patients who show evidence of the disease in other organs. Approximately one-third of the patients diagnosed with CMV retinitis could develop systemic CMV disease, but, in general, these disease manifestations are short-lived and require short courses of therapy.

In July 1997, the Company entered into an agreement with CIBA Vision Corporation (a Novartis subsidiary) granting CIBA Vision exclusive worldwide distribution rights for fomivirsen. See "Collaborative Agreements - CIBA Vision."

ISIS 13312. ISIS 13312, a second generation compound, is based on novel, improved antisense chemistry and is being tested in a Phase I clinical trial as a local treatment for CMV retinitis in AIDS patients. Based on the results of preclinical studies, ISIS 13312 appears to be less toxic and more stable than fomivirsen. Because of this improved profile, ISIS 13312 may be able to be dosed less frequently than fomivirsen. CIBA Vision has an option to market and distribute ISIS 13312 exclusively worldwide. See "Collaborative Agreements - CIBA Vision."

INFLAMMATORY DISEASES

Cell adhesion molecules make up a large family of related proteins and represent targets for treating inflammatory diseases. Inflammation is a key component of a large number of acute and chronic diseases. Although inflammation is part of a normal localized protective response that the human body uses to destroy infectious agents or repair injured tissue, disruptions of normal inflammatory responses often lead to inflammatory diseases. These inflammatory responses result in or contribute to a diverse set of diseases that can affect many organs of the body ranging from the skin to the brain. Common inflammatory diseases include rheumatoid arthritis, psoriasis, asthma and inflammatory bowel disease. Inflammation also occurs as a result of burn, shock or organ transplantation.

Some cell adhesion molecules are expressed on the surface of endothelial cells which line the blood vessels of the body during periods of heightened inflammatory or immune system response. These adhesion molecules act as anchors for various types of immune cells circulating in the blood.

Once the immune cells are anchored to the endothelial cells by the cell adhesion molecules, these immune cells can migrate between the endothelial cells, leave the blood vessels and travel into tissues and organs where they can cause inflammation. Left unchecked, these processes can result in acute and chronic tissue damage and disease. Current anti-inflammatory agents and drugs that suppress the immune system decrease the symptoms of inflammation but do little to change the course of the underlying disease, or do so at the risk of substantial toxicity. However, a drug that stops the production of cell adhesion molecules may prevent the migration of immune cells from the blood vessels into tissue and therefore modify the disease process with a more acceptable toxicity profile than do currently available therapies.

Isis has focused on a number of targets in its cell adhesion molecule program. While we have identified preclinical lead compounds targeting vascular cell adhesion molecules ("VCAM-1") and platelet-endothelial cell adhesion molecules ("PECAM-1") that could also represent novel approaches to treat chronic inflammatory diseases, the Company is currently focused on the intercellular adhesion molecule ("ICAM") family and in particular, ICAM-1. Unlike other adhesion molecules, ICAM-1 facilitates the migration of immune cells involved in both chronic and acute inflammation, allowing Isis to target both conditions. Over-expression of ICAM-1 is specifically involved in a wide variety of inflammatory disorders, such as rheumatoid arthritis, asthma, psoriasis, organ transplant rejection and inflammatory bowel disease. While it is unlikely that over-expression of ICAM-1 is a cause of these disorders, ICAM-1 is thought to contribute to the pathology of these diseases or conditions.

In 1995, Isis and Boehringer Ingelheim agreed to combine their respective programs in the area of cell adhesion to form a jointly managed and funded effort. This partnership combines Boehringer Ingelheim's significant expertise in cell adhesion biology and its small molecule and monoclonal antibody-based drug discovery efforts, including its state-of-the-art analysis technology, with Isis' antisense and combinatorial drug discovery programs. The collaboration uses these multiple drug discovery programs to identify compounds that limit the disease-related functions of cell adhesion molecules.

ISIS 2302. ISIS 2302, the Company's most advanced compound in its cell adhesion program, selectively inhibits ICAM-1 gene expression. In Phase I testing of ISIS 2302 in healthy volunteers, the compound was well tolerated at all doses. The Company initiated Phase II trials in 5 disease indications: rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis and prevention of renal transplant rejection. The Phase II studies involve 20 to 40 patients each and, in general, are randomized and placebo-controlled. We will choose indications for further development of ISIS 2302 based on results from these studies.

Crohn's disease is a serious inflammatory disease that affects the intestines and other parts of the digestive tract. A patient with Crohn's disease suffers chronic and often severe episodes of diarrhea, abdominal pain, rectal bleeding and fever. Approximately 500,000 people worldwide are currently estimated to be afflicted with Crohn's disease. In a randomized, double-blinded, placebo-controlled 20-patient Phase II study of patients with Crohn's disease, 15 patients were treated with ISIS 2302 and 5 patients received a placebo. ISIS 2302 was administered every other day for 26 days (13 doses) by 2-hour intravenous infusion. At the end of the one-month treatment period, 7 of 15 patients treated with ISIS 2302 experienced disease remission (measured by a Crohn's Disease Activity Index score of below 150) compared to zero patients in remission in the placebo group. The duration of the remissions was prolonged, with 5 of 7 remitting patients still in remission at the end of the 6-month trial. Results of this study also showed a statistically significant lowering of steroid use in the ISIS 2302 treated group compared to the placebo treated group. The results also showed favorable trends both in the Endoscopic Index of Severity (EIS), based on colonoscopic examination, and in the Inflammatory Bowel Disease Questionnaire (IBDQ), a quality of life scale. Based on the results of this study, Isis and Boehringer Ingelheim decided to initiate a pivotal quality trial of ISIS 2302 in Crohn's disease. That trial is progressing. The full development program for ISIS

2302 in Crohn's disease includes dose regimen studies intended to enhance the commercial potential of the drug. The program may be expanded to include additional pivotal studies in 1999 based on analysis of the data from ongoing trials.

In the rheumatoid arthritis study, enrollment was increased from 20 to 40 patients to provide more definitive information on this disease. The last patient was enrolled in November 1997. We are currently in the follow-up period for this study. The decision to proceed with development in rheumatoid arthritis using ISIS 2302 or a second-generation ICAM-1 inhibitor will depend upon the results of this study.

Data from the psoriasis study showed that about one half of the patients had some clinical improvement but that the effect was of short duration. Based on these results, as well as animal studies using a topical formulation of ISIS 2302, we have decided to develop a topical formulation of ISIS 2302 for psoriasis. In animal studies, we have demonstrated good drug penetration of skin, with strong evidence that ICAM- 1 would be inhibited in skin cells with a topical formulation of ISIS 2302. We will begin evaluating a topical treatment approach with both ISIS 2302 and a second-generation ICAM-1 compound in 1998.

In ulcerative colitis study, enrollment of steroid-dependent patients is proceeding slowly, as this patient population will often choose surgery, which can be curative, over long-term steriod use. We are exploring local delivery of ISIS 2302 directly to the colon via retention enema, a common treatment for inflammatory bowel disorders. Animal sudies have demonstrated significant local absorption into the

colon, suggesting that this route of delivery could be appropriate for ulcerative colitis patients who have failed aminosalicylates but who wish to avoid steroid use.

The Phase II study in kidney transplant rejection is also proceeding at a pace mandated by the regulatory authorities, as they carefully monitor clinical studies in this patient population. We and Boehringer Ingelheim are exploring local delivery to the lung for asthma with both ISIS 2302 and analogs of ISIS 2302 incorporating second generation antisense chemistry.

CANCER

Much of Isis' work in the area of cancer is focused on specific targets within multigene families believed to be involved in both normal and abnormal cell differentiation and cell growth. Members of multigene families, called isotypes, are extremely similar to one another at the protein level but most likely serve different biological functions. Since traditional drugs are not specific enough to inhibit one isotype within a family without affecting the function of the other related isotypes, it has been difficult to determine the functional differences among them. There is growing evidence that certain isotypes might be involved in abnormal cell differentiation or proliferation. Antisense drug discovery technology exploits the differences among the isotypes at the mRNA level to design drugs that can inhibit specific isotypes. Selective inhibition of a single isotype may result in less toxicity. Much of Isis' work has focused on multigene families in the signal transduction pathway, the method by which various cellular and extra cellular proteins communicate information necessary for cell function and growth. Disruptions in the production or behavior of signal transduction proteins are involved in numerous proliferative disorders, including cancer.

Clinical trials of Isis' anticancer compounds demonstrated that antisense drugs can be effective cancer therapeutics. In these trials, Isis' compounds were well tolerated, with none of the serious side effects associated with standard cancer chemotherapies such as bone marrow or immune system suppression, gastrointestinal distress and hair loss.

ISIS 3521. ISIS 3521 is an antisense compound in Phase II clinical development which inhibits the production of one particular isotype (the [Greek

alpha] isotype) of protein kinase C. PKC is a key enzyme in signal transduction, and PKC isotypes are associated with both normal and abnormal cell growth. Isis has been able to specifically inhibit the production of the PKC-[Greek alpha] isotype without inhibiting the production of other isotypes, thus allowing the inhibition of the isotype believed to be involved in abnormal cell growth without inhibiting the isotypes required for healthy cells to grow.

In specially developed mice with compromised immune systems in which human tumors can be grown (called nude mouse xenograft models), ISIS 3521 showed strong inhibition of tumor growth.

The Phase I studies included 56 patients with various types of cancer that had not responded to standard treatment. In one study, 36 patients received the drug via a 2-hour infusion 3 times per week for 3 weeks, with redosing every 4 weeks. In a second study, 20 patients received the drug via a 21-day continuous infusion for 3 weeks repeated every 4 weeks. The primary endpoint of the Phase I trials was safety, and all patients were assessed for antitumor effects. In these Phase I trials, the drug was well-tolerated by patients with no significant side effects. We also saw preliminary evidence of anticancer activity. In the short infusion study, 1 patient with lymphoma experienced a partial response (defined as a greater than 50% reduction in measurable disease) that has continued for more than 16 months from the start of therapy. Another patient with lymphoma has had a partial response lasting more than 8 months, and 1 patient with non-small cell lung cancer has experienced disease stabilization for 8 months. In the continuous infusion study, 3 of 4 patients with ovarian cancer showed a decrease in disease. One patient, whose abdominal mass had doubled in size in the month prior to entering the study, experienced a partial response for over 11 months before progressing. One patient experienced a 40% decrease in CA-125, an ovarian tumor marker, for over 5 months, and 1 patient experienced a 75% decrease in CA-125 for more than 7 months.

We initiated Phase II clinical trials in the third quarter of 1997. In the Phase II trials ISIS 3521 is being evaluated in both single-agent and combination studies in patients with a variety of solid tumors, including ovarian, prostate, breast, brain, colon and lung cancers, and melanomas.

We are developing ISIS 3521 as part of our antisense research and development collaboration with Novartis. Isis also has additional PKC-[Greek alpha] inhibitors in preclinical development which incorporate second generation chemistry, and which have the potential for increased safety and more convenient dosing, possibly including oral delivery. Isis also has lead compounds that inhibit 2 isotypes of the PKC family, including PKC-[Greek epsilon], believed to be involved in cancer and other diseases.

ISIS 5132. ISIS 5132 is an antisense compound which inhibits the expression of C-raf kinase, another molecular target involved in cell signaling. C-raf kinase is a member of the raf kinase multi-gene family and is associated with abnormal cell growth. ISIS 5132 selectively inhibits C-raf kinase without inhibiting the production of other members of that multigene family. Studies of ISIS 5132 in cell culture and in nude mouse xenograft models using human tumor cells show that ISIS 5132 inhibits expression of the target C-raf gene.

In Phase I clinical trials, ISIS 5132 was very well-tolerated. Several patients in this trial experienced disease stabilization. In the 2-hour infusion study, 1 patient with colon cancer experienced a decrease in CEA, a colon cancer marker, with no growth in tumor for approximately 7 months. Another patient with kidney cancer experienced disease stabilization for more than 9 months and continues to be on study. In the continuous infusion study, 1 patient with pancreatic cancer experienced disease stabilization for 7 months and continues on study, 1 patient with kidney cancer experienced disease stabilization for 9 months, and 1 patient with ovarian cancer had a 97% drop in CA-125 after 6 months.

We initiated Phase II clinical trials of ISIS 5132 in the fourth quarter of 1997. In the Phase II trials ISIS 5132 is being evaluated as a

single-agent in studies of patients with a variety of solid tumors, including prostate, breast, ovarian, pancreatic, colon and both small-cell and non-small cell lung cancers. We will also conduct studies examining the use of ISIS 5132 in combination with approved chemotherapies in 1998.

ISIS 2503. Substantial evidence exists supporting a direct role for ras gene products in the development and maintenance of human cancer. Ras proteins are involved in passing information between cells. Ras, in both normal and mutated forms, is associated with abnormal cell growth and, as such, is associated with cancer. ISIS 2503, a potent selective inhibitor of Harvey ras, has been shown to inhibit abnormal cell growth by inhibiting expression of ras genes in cell culture and animal models. ISIS 2503 has also inhibited the growth of multiple different human cancers in nude mouse xenograft models. In the fall of 1997, we initiated Phase I clinical trials of ISIS 2503. The Phase I trial involves patients with a variety of solid tumors that have not responded to standard cancer therapies.

HUMAN IMMUNODEFICIENCY VIRUS ("HIV")

ISIS 5320 was discovered through the Company's combinatorial drug discovery program to prevent replication of HIV. Isis has decided not to pursue further development of this compound. In the Phase I trial, completed in late 1997, ISIS 5320 was well-tolerated but antiviral activity in the regimen studied was minimal. We had initiated this small trial based on promising anti-HIV activity demonstrated in vitro and in animal models, but we knew that the drug would have to demonstrate extraordinary antiviral activity to justify full development. In light of the other product opportunities in our pipeline, we decided not to invest further in development. The National Cancer Institute, which funded much of the preclinical development of ISIS 5320, has the option to do additional work on the compound.

RESEARCH PROGRAMS

Isis combines its core technology programs in medicinal chemistry, RNA biochemistry, and molecular and cellular biology with molecular target-focused drug discovery efforts to design drug candidates. The goal of Isis' target-based research programs is to identify antisense and combinatorial

drug candidates to treat diseases for which there are substantial markets and for which there is a need for better drugs. In addition, Isis' research programs focus on identifying next-generation compounds to serve as backup compounds to its current products in development and development candidates. Isis' combinatorial drug discovery program is currently focused both on cell adhesion molecules in connection with its collaboration with Boehringer Ingelheim and on identifying broad-spectrum antibacterial agents with a focus on important drug-resistant infections.

Isis' core technology programs can support multiple target-based antisense research programs without significantly increasing costs. Through these programs, Isis can efficiently explore numerous disease targets and identify the best lead compounds to advance into preclinical development. Isis is currently pursuing antisense and combinatorial drug discovery programs focused on various anti-viral and anti-bacterial targets, inflammatory disease targets, and other key molecular targets that might play critical roles in cancer.

COLLABORATIVE AGREEMENTS

Isis' strategy is to use alliances with other companies and equity-based financing to increase its financial resources, reduce risk, and retain an appropriate level of ownership of products currently in development. Through alliances with other major pharmaceutical companies, Isis can obtain funding, expand existing programs, learn of new technologies, and gain additional expertise in developing and marketing products. Isis intends to continue this strategy.

NOVARTIS

Isis began its research and development collaboration with Ciba-Geigy Limited ("Ciba") in 1990. In 1996, Ciba merged with Sandoz, Ltd. to form a new company called Novartis. As of February 27, 1998, Novartis owned approximately 8% of Isis' outstanding Common Stock.

The research alliance currently focuses on PKC-[Greek alpha] and C-raf kinase and other undisclosed targets (the "Novartis Targets"). Isis has committed substantial resources to discover and investigate antisense compounds that inhibit the Novartis Targets. Novartis provides financial support for Isis research relating to these targets. Novartis has also committed substantial resources of its own to the research of antisense drugs. Either company may end the collaborative research program beginning in September 1998, with certain exceptions. We are in the process of negotiating an expanded collaborative research program with Novartis..

Novartis has the option, which can be exercised before clinical development begins, to obtain an exclusive license to develop, manufacture, use, and market compounds produced by the alliance that inhibit the Novartis Targets (the "Novartis Compounds"). If Novartis exercises its option, Isis and Novartis will develop the Novartis Compounds at Novartis' expense. Novartis will pay Isis for achievement of certain milestones as the first 2 Novartis Compounds are developed against each Novartis Target. With certain exceptions, in the event that Novartis fails to exercise its option to license any Novartis Compound, it forfeits all rights to the compound. Novartis has exercised its option with respect to ISIS 5132 and ISIS 3521. At Novartis' expense, Isis is conducting clinical development of these compounds. See "Products Under Development - Cancer - ISIS 3521; ISIS 5132."

Novartis will pay Isis royalties on the sale of any Novartis Compound. Isis has the right to commercially manufacture ISIS 5132 and ISIS 3521 for additional royalties. Manufacturing of additional Novartis Compounds will be determined based on cost, quality, and supply factors. If Isis is the manufacturer, we will receive additional royalties. Both Novartis and Isis have the right to terminate the collaborative research program beginning in September 1998. Under certain circumstances Novartis may terminate the research program earlier.

BOEHRINGER INGELHEIM

In July 1995, Isis and Boehringer Ingelheim formed an alliance to combine the clinical development and research programs of both companies in the field of cell adhesion. Isis contributes its

expertise in antisense and combinatorial drug discovery and Boehringer Ingelheim contributes its ongoing program in cell adhesion biology and small molecule library screening capabilities. Both companies provide ongoing funding for the combined research and development program. Either party may terminate the funding requirements under the collaboration agreement if, at the end of 5 years, there are no compounds being developed or commercialized jointly.

As of February 27, 1998, Boehringer Ingelheim owned approximately 9% of Isis' outstanding Common Stock. In addition to funding one- half of the collaboration's research and development, Boehringer Ingelheim will make additional investments in Isis as certain development milestones are met. Boehringer Ingelheim has already paid Isis a milestone payment of $10 million for the completion of the first Phase II clinical trial of ISIS 2302 in Crohn's disease. It also provided Isis with a $40 million line of credit, which is available under certain circumstances. As of December 31, 1997, outstanding borrowings under this line of credit totaled $ 22.6 million.

The partnership includes development of ISIS 2302, an antisense inhibitor of ICAM-1, and multiple other preclinical and research compounds targeting other adhesion molecules. Isis and Boehringer Ingelheim will split the operating profits associated with all future products of the partnership. If a partner chooses not to continue to fund its share of the development

expenses for a compound, it will receive a certain amount of royalties on any future sales of such compounds rather than a split of operating profits. Boehringer Ingelheim will market the first 2 drugs resulting from the collaboration. Both companies will agree on commercialization responsibilities for any products to follow.

ISIS 2302 is in a pivotal quality trial for Crohn's disease and Phase II clinical trials for 4 other indications. This compound is being developed by an Isis-led project team as part of the collaboration See "Products Under Development - Inflammatory Diseases."

CIBA VISION

In July 1997, the Company entered into an agreement with CIBA Vision, granting it exclusive worldwide distribution rights for fomivirsen. Under the terms of the agreement, Isis will receive $20 million in pre-commercial fees and milestones through the time of regulatory approval in the United States and Europe. In the third quarter of 1997, Isis received the first $5 million of the pre-commercial fees and milestones. While CIBA Vision will market and sell fomivirsen worldwide, we will manufacture and sell fomivirsen to CIBA Vision, at a price that will allow us to share the commercial value of the product with CIBA Vision. An NDA filing for fomivirsen is planned for early 1998. CIBA Vision also has the option to acquire the exclusive license to market and distribute our second generation antisense compound to treat CMV retinitis, ISIS 13312, which is currently in preclinical development. See "Products Under Development - Cytomegalovirus (CMV) Retinitis."

MANUFACTURING

In the past, production of chemically modified oligonucleotides like those used in the Company's research and development programs, was generally expensive and difficult, except in small quantities. As a result, Isis dedicated significant resources to focus on ways to improve manufacturing capacity. Because all oligonucleotide compounds are made of variants of the same nucleotide building blocks and are produced using the same types of equipment, Isis found that the same techniques used to efficiently manufacture one oligonucleotide drug product proved helpful in improving the manufacturing processes for many other oligonucleotide products. Through the development of several Isis-owned chemical processes for scaling up manufacturing capabilities, we have been able to greatly reduce the cost of producing oligonucleotide compounds. For example, we have significantly reduced the cost of raw materials, while at the same time greatly increasing our capacity to make the compounds. We have both internal programs and outside collaborations with various industry vendors to allow for even greater production.

We have sufficient manufacturing capacity to meet both current and future research and clinical needs both for ourselves and for our partners. The Company also believes that it has, or will be able to develop or acquire, sufficient supply capacity to meet its anticipated commercial needs. Isis also believes that with reasonably anticipated benefits from increases in scale, we will be able to manufacture antisense compounds at commercially competitive prices.

In March 1998, Isis established an antisense oligonucleotide manufacturing collaboration with Zeneca Life Science Molecules ("Zeneca LSM"), a leading supplier of chemical and biological compounds to the pharmaceutical and biotechnology industries. Access to an alternate manufacturing source will provide greater flexibility in production scheduling and will reduce the Company's risk of dependence on a single manufacturing site for all of its clinical needs. Under the terms of the 5 year agreement, Zeneca LSM will supplement Isis' primary manufacturing facility in producing antisense oligonucleotides for use in clinical trials. The agreement specifies that Isis will have Zeneca LSM manufacture a certain portion of the drug supplies required for its clincal trials. Isis is not required to make any capital investment to create this manufacturing capability.

GOVERNMENT REGULATION

The Company's manufacture and potential sale of therapeutics are subject to extensive regulation by United States and foreign governmental authorities. 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. Pharmaceutical manufacturing facilities are also regulated by state, local and other authorities. Obtaining approval from the FDA and other regulatory authorities for a new therapeutic may take several years and involve substantial expenditures. Moreover, ongoing compliance with these requirements can require the expenditure of substantial resources. Difficulties or unanticipated costs may be encountered by the Company or its licensees or marketing partners in their respective efforts to secure necessary governmental approvals, which could delay or preclude the Company or its licensees or marketing partners from marketing their products.

In addition to regulations enforced by the FDA, the Company is 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. The Company believes that it is in compliance in all material respects with applicable laws and regulations.

COMPETITION

For many of their applications, antisense based drugs will be competing with existing therapies for market share. In addition, a number of companies are pursuing the development of oligonucleotide-based technology and the development of pharmaceuticals utilizing such technology. These companies include specialized pharmaceutical firms and large pharmaceutical companies acting either independently or together with biopharmaceutical companies. Many of the Company's existing or potential competitors have substantially greater financial, technical and human resources than the Company and may be better equipped to develop, manufacture and market products. In addition, many of these companies have extensive experience in preclinical testing and human clinical trials. These companies may develop and introduce products and processes competitive with or superior to those of the Company. Furthermore, academic institutions, government agencies and other public and private organizations conducting research may seek patent protection and may establish collaborative arrangements for product and clinical development.

The Company's products under development address numerous markets. The Company's competition will be determined in part by the diseases for which the Company's compounds are developed and ultimately approved by regulatory authorities. For certain of the Company's potential products, an important factor in competition may be the timing of market introduction of its or competitive products. Accordingly, the relative speed with which Isis can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market is expected to be an important competitive factor. The Company expects that competition among products approved for sale will be based, among other things, on product efficacy, safety, reliability, availability, price and patent position.

The development by others of new treatments for the diseases for which the Company is developing compounds could render the Company's compounds non-competitive or obsolete. Furthermore, because of the fundamental differences between antisense and other technologies, there may be applications for which the products of one technology are superior to those of another. Isis is aware of several companies with late-stage compounds in development for diseases targeted by the Company.

The Company's competitive position also depends upon its ability to attract and retain qualified personnel, obtain patent protection or otherwise develop proprietary products or processes and secure sufficient capital resources for the often substantial period between technological conception and commercial sales.

EMPLOYEES

As of February 27, 1998, Isis employed 338 individuals, of whom 135 hold advanced degrees. A significant number of the Company's management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. Isis believes that it has been highly successful in attracting skilled and experienced scientific personnel; however, competition for such personnel is intensifying. None of the Company's employees is covered by collective bargaining agreements, and management considers relations with its employees to be good.

EXECUTIVE OFFICERS

The executive officers of the Company and their ages as of February 28, 1997 are as follows:

STANLEY T. CROOKE, M.D., PH.D.... 52
Chairman of the Board and Chief Executive Officer

Dr. Crooke was a founder of the Company and has been its Chief Executive Officer and a director since January 1989 and served as its President from January 1989 to May 1994. He was elected Chairman of the Board in February 1991. From 1980 until January 1989, Dr. Crooke was employed by SmithKline Beckman Corporation, a pharmaceutical company, most recently as President of Research and Development of SmithKline & French Laboratories. Dr. Crooke is Chairman of the Board of GeneMedicine, Inc. and a director of SIBIA Neurosciences, Inc., both biotechnology companies, and EPIX Medical, Inc., a developer of magnetic resonance imaging contrast agents. He is also an adjunct professor of pharmacology at the Baylor College of Medicine and the University of California, San Diego.

DANIEL L. KISNER, M.D.... 51
President and Chief Operating Officer

Dr. Kisner has served as a director of the Company since March 1991, Chief Operating Officer since February 1993 and President since May 1994. He was Executive Vice President of the Company from March 1991 until May 1994. From December 1988 until March 1991, he was a Division Vice President of Pharmaceutical Development for Abbott Laboratories, a pharmaceutical company. He is also a director of Anesta Corporation, a drug delivery company.

B. LYNNE PARSHALL.... 42
Executive Vice President, Chief Financial Officer and Secretary

Ms. Parshall has served as Executive Vice President since December 1995, Chief Financial Officer of the Company since June 1994, and Secretary since November 1991. From February 1993 to December 1995, she was a Senior Vice President of the Company, and from November 1991 to February 1993, she was a Vice President of the Company. Prior to joining Isis, Ms. Parshall practiced law at Cooley Godward LLP, counsel to the Company, where she was a partner from 1986 to 1991. Ms. Parshall served as Vice President of Business Development of Biotrack, Inc., a medical device company, during 1988 and 1989.

RISK FACTORS

Please consider the following risk factors carefully in addition to the other information contained in this Report.

UNCERTAINTY ASSOCIATED WITH CLINICAL TRIALS

We must conduct time-consuming, extensive and costly clinical trials, in compliance with FDA regulations, to show the safety and effectiveness ("efficacy") of each of our drug candidates, as well as its optimum dosage, before the FDA can approve a drug candidate for sale.

To begin the process, preclinical studies are conducted, first in the research laboratory and then in animals, to identify potential safety problems. For certain diseases, there are animal models that we believe will predict the effects of the drug candidate in humans. For these diseases, a drug candidate is first tested in such an animal model. For several of our drug candidates, no such animal model exists, so evidence of the drug candidate's efficacy must wait until testing on humans. If the research and preclinical development support further development, we must then submit an Investigational New Drug ("IND") application to the FDA to obtain authorization for human clinical testing. However, our IND application may not be granted by the FDA.

Clinical trials are typically conducted in 3 sequential phases, although the phases may overlap. In Phase I, which typically involves giving the drug to healthy human subjects before giving it to patients, the drug candidate is tested for safety and tolerance. Phase II typically involves studies in a somewhat larger population of diseased patients to identify possible negative effects and safety risks, to begin gathering preliminary effectiveness data and to investigate possible dose sizes and schedules. Phase III trials further evaluate the drug's effectiveness and further test for safety within an expanded patient population. Each trial follows certain standards and procedures set out in a scientific document, called a protocol, that describes the objectives of the study, the standards to be used to monitor safety and the efficacy criteria to be measured. Each proposed study protocol must be submitted to the FDA as part of the IND. In addition, in the United States, each clinical study is observed by an independent Institutional Review Board ("IRB"). The IRB will consider, among other things, ethical factors, the safety of human subjects and patients and the possible liability of the study center. Foreign countries have similar protocol review procedures and review boards.

Even when human clinical trials are authorized, such testing of any of our current or future drug candidates may not be completed within the specified time period, if at all. The rate of patient enrollment is a critical factor in determining whether a clinical trial will be completed. Patient enrollment depends upon many different factors, including the number of patients suffering from the disease, the type of procedure involved in the trial, whether patients live near the clinical site and if patients meet the criteria to allow them to participate in the study. Delays in planned patient enrollment may result in significant increased costs and delays to the Company.

We, the FDA or foreign regulatory agencies may also suspend clinical trials at any time if it is shown that the subjects or patients participating in such trials are being exposed to unacceptable health risks. Clinical testing may show any current or future drug candidate to be unsafe or ineffective, and the FDA or foreign regulatory agency might not approve any such product.

Once the clinical trials are completed, data from preclinical testing and clinical trials are submitted to the FDA in an NDA in order to obtain approval to sell the drug. Preparing an NDA involves considerable data collection, verification, analysis and expense. The NDA often takes months to prepare. NDA approval may not be granted on a timely basis, if at all. A number of factors are weighed by the FDA in the approval process, including the severity of the disease, whether other treatments are currently available and the risks and benefits demonstrated in clinical trials. The FDA may deny an NDA if applicable regulatory criteria are not satisfied. The FDA may also require additional testing or information prior to approval, or approve the application but require post-marketing testing and surveillance to monitor the safety of the drug. Quality control and appropriate manufacturing procedures are also conditions for NDA approval. We must submit a similar separate application to foreign regulatory agencies for their review in order to obtain approval to sell the drug in other countries.

NO ASSURANCE OF REGULATORY APPROVAL

The Company's ongoing research and development activities, as well as the production and marketing of the Company's products, are regulated by many federal, state and local governmental authorities in the United States. Similar regulatory authorities exist in other countries where we intend to test and market our products. Various federal, state and foreign statutes also affect the labeling, storage and record keeping of the drug. The regulatory process, which includes preclinical and clinical testing of each drug candidate to establish its safety and effectiveness, can take many years and is very expensive. Data obtained from preclinical and clinical activities can be interpreted in different ways, which could delay, limit or prevent FDA or other regulatory approval. If FDA drug approval policies change during the period of product development and regulatory review, delays or rejections can also result. The Company, its licensees or its marketing partners may encounter similar delays, difficulties or unanticipated costs in foreign countries. Therefore, even after spending significant amounts of time, money, and effort, regulatory approval may not be obtained for drugs developed by the Company in the United States or in other countries in which it wishes to sell those drugs.

Even if regulatory approval of a drug is granted, the approval may limit the drug to certain uses or "indications." Additional clinical trials may be necessary to obtain approval for the use of a drug for any additional indications. An approved drug, its manufacturer and its manufacturing facilities are also subject to continual review and periodic inspections by the FDA or foreign regulatory agencies, even after the drug is on the market. Manufacturers must spend considerable time, money and effort, especially in the areas of production and quality control, to comply with FDA or foreign manufacturing regulations. Later discovery of previously unknown problems with a product, manufacturer or facility may result in restrictions being placed on such product or manufacturer, including forcing a withdrawal of the product from the market. Additionally, if the drug product manufacturer's facility is not approved or if approval is withdrawn, it can take a considerable amount of time to obtain recertification or to certify a new facility. The Company's failure to comply with applicable regulatory requirements could, among other things, result in fines, suspensions of regulatory approvals, product recalls, operating restrictions and criminal

prosecution. Further, additional government regulations may be created in the future that could prevent or delay regulatory approval of our products.

DEPENDENCE ON COLLABORATIVE PARTNERS

We have relied on certain established pharmaceutical companies interested in our technology and products to pay for a portion of our research and development expenses. We have entered into research, development and distribution agreements with these collaborative partners whereby the partners provide money in exchange for certain research services, product rights and/or marketing rights related to the products or targets involved. Under certain of these agreements, the collaborative partner has some responsibility for conducting preclinical testing and human clinical trials and for preparing and filing the submission for regulatory approval of the drug candidate with the FDA and foreign regulatory agencies. In addition, certain of these agreements provide for Isis to receive royalties or other revenues based on sales of products developed and/or marketed by its corporate partners.

If any collaborative partner fails to successfully develop or sell any product in which we have rights, our business may be negatively affected. While we believe that our collaborative partners will have sufficient motivation to continue their funding, development and commercialization activities, we cannot be sure that any of these collaborations will be continued or result in successfully commercialized products. The failure of a corporate partner to continue funding any particular program could delay or stop the development or commercialization of any products resulting from such program. In addition, collaborative partners may be pursuing other technologies or developing other drug candidates either on their own or in

collaboration with others, including our competitors, to develop treatments for the same diseases targeted by our own collaborative programs. We also may wish to rely on additional collaborative arrangements to develop and commercialize our products in the future. However, we may not be able to negotiate acceptable collaborative arrangements in the future, and, even if successfully negotiated, the collaborative arrangements themselves may not be successful. Our current collaboration agreement with Novartis is scheduled to terminate in September 1998. While we are currently negotiating another collaboration agreement with Novartis which would extend and expand the scope of our collaboration, we may not be able to negotiate acceptable terms for that agreement.

EARLY STAGE OF DEVELOPMENT; TECHNOLOGICAL UNCERTAINTY

Isis is still at an early stage of development. Most of our resources are dedicated to applying molecular biology and medicinal chemistry to the discovery and development drug candidates based upon antisense technology. Although we have a pipeline of promising antisense drug candidates, with 6 such products in clinical trials, as yet we have no products on the market, and there are no drugs using antisense technology currently on the market. Laboratory results obtained in preclinical studies do not necessarily indicate the results that will be obtained in later stages of preclinical development or in human clinical testing. For example, we are attempting to develop products for certain diseases for which no appropriate animal model that might predict effectiveness currently exists. As a result, drug candidates for these diseases must advance at least to Phase II human clinical trials before we will have evidence of effectiveness outside of the laboratory. Drugs discovered by the Company may not effectively combat the targeted disease and, even if they work, may not be commercially successful.

CONTINUING OPERATING LOSSES

Because of the nature of the business of drug discovery and development, our expenses have exceeded our revenues since the Company was founded in January 1989. At December 31, 1997, the Company's accumulated deficit was approximately $154 million. Most of the losses have resulted from costs incurred in connection with the Company's research and development programs and from general and administrative costs associated with the Company's growth and operations. These costs have exceeded the Company's revenues, most of which has come from collaborative arrangements, interest income and research grants. We have received no revenues from product sales. We expect to incur additional operating losses over the next several years and we expect losses to increase as our preclinical

testing and clinical trial efforts continue to expand. Our ability to ever achieve profitability depends upon whether we are able to obtain regulatory approvals for our products, enter into agreements for product development and commercialization and develop the ability to manufacture and sell our products successfully.

FUTURE CAPITAL NEEDS; UNCERTAINTY OF ADDITIONAL FUNDING

The Company believes that it has enough money to satisfy its needs for at least the next 2 years. The Company's future capital requirements will depend on many factors, including continued scientific progress in its research, drug discovery and development programs; the size of these programs and progress with preclinical and clinical trials; the time and costs involved in obtaining regulatory approvals; the costs involved in filing, prosecuting and enforcing patent claims; competing technological and market developments; changes in existing collaborative relationships and the ability of the Company to establish and maintain additional collaborative arrangements. Need for additional funding will also depend upon the cost of manufacturing products on a larger scale and the ability of the Company to establish and maintain effective marketing and sales activities and arrangements. If the Company finds that it does not have enough money, additional funds may be raised,

including through public or private financing. Additional financing may not be available, or, if available, may not be on acceptable terms. If additional funds are raised by issuing equity securities, the shares of existing stockholders will be subject to further dilution and share prices may decline. If adequate funds are not available, the Company may be required to cut back on one or more of its research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others. These arrangements may require the Company to give up rights to certain of its technologies, product candidates or products.

LIMITED LARGE-SCALE MANUFACTURING EXPERIENCE

Our ability to operate profitably will depend in part on our ability to manufacture our drug products, or to have another company manufacture our products, at a cost low enough to enable us to charge a competitive price to buyers. To successfully establish additional commercial manufacturing capability on a large scale, we must improve our manufacturing processes and reduce our product costs. The manufacture of sufficient quantities of new drugs is typically a time-consuming and complex process. Pharmaceutical products based on chemically modified oligonucleotides have never been manufactured on a large commercial scale. There are a limited number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

POSSIBLE OBSOLESCENCE DUE TO TECHNOLOGICAL CHANGE; COMPETITION

Certain companies, both private and publicly traded, are conducting research and development activities with antisense technology and products. We believe that the investigation of the potential of antisense drugs will continue and may increase as these drug design and development techniques become more widely understood. Our competitors are engaged in all areas of drug discovery in the United States and other countries, are numerous, and include, among others, major pharmaceutical and chemical companies, specialized biopharmaceutical firms, universities and other research institutions. Our competitors may succeed in developing antisense drugs or other new therapeutic drug candidates that are more effective than any drug candidates that we have been developing. Such competitive development could make our technology and products obsolete or non-competitive before we have had enough time to recover our research, development or commercialization expenses.

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. Furthermore, if we are

permitted to sell products, we will also be competing with respect to manufacturing efficiency and marketing capabilities, areas in which we have limited or no experience.

DEPENDENCE ON PATENTS AND PROPRIETARY RIGHTS

The Company's success will depend in part on its ability to obtain patent protection for its products both in the United States and in other countries. The Company files applications, as appropriate, for patents covering both its products and processes. As of December 31,1997, Isis had been issued more than 90 United States patents and more than 70 foreign patents, had received 27 U.S. notices of allowance and had filed more than 250 patent applications in the United States and counterparts of certain of these applications in many foreign countries. Patents may not issue from any of these applications. Patent applications in the United States are maintained in secrecy until the patents actually issue, and publication of discoveries in the

scientific or patent journals tends to lag behind the date of the actual discoveries by several months. For these reasons, the Company cannot be certain that it was the first creator of inventions covered by its pending patent applications or that it was the first to file patent applications for such inventions. Further, the claims allowed under any issued patents may not be broad enough to protect the Company's proprietary position in its technology. In addition, even issued patents may be challenged, invalidated or circumvented by third parties, and the rights granted may not provide us with competitive advantage.

We must also avoid both infringing patents issued to our competitors and breaching the technology licenses upon which our products might be based. While we are aware of patent applications and patents belonging to competitors, there is always a possibility that a competitor's patent might require us to alter our products or processes, pay licensing fees or stop certain activities. We may not be able to obtain a license to other required technology or, if obtainable, such technology may not be available at reasonable cost. Such developments would cause financial harm to us.

Costly litigation may also be necessary to enforce any patents issued to us and/or to determine the scope and validity of others' proprietary rights in court or in administrative proceedings. In addition, to determine the priority of inventions, we may find it necessary to participate in interference proceedings declared by the U. S. Patent and Trademark Office or in opposition, nullity or other proceedings before foreign agencies in connection with any of our existing or future patents or patent applications. Further, we may find it necessary to participate, at substantial cost, in International Trade Commission proceedings to reduce or stop importation of goods that would compete unfairly with our products. If required, any of the proceedings described above will result in substantial cost to the Company.

We also rely on trade secrets and proprietary know-how, which we try to protect, in part, by insisting upon confidentiality agreements with our corporate partners, collaborators, employees and consultants. However, these agreements may be breached, and we may not have adequate remedies for any breach. If this happens, our trade secrets may become known or be independently discovered by competitors.

ABSENCE OF SALES AND MARKETING CAPABILITIES

We have no experience in sales, marketing or distribution. To market any of our products directly, we must develop an expert marketing and sales force capable of supporting product distribution. We may not be able to build such a sales force at all, or at a reasonable cost, and if we do, our direct sales and marketing efforts may not be successful. As with any new product, the Company's products may not achieve market acceptance in place of existing treatments.

UNCERTAINTIES ASSOCIATED WITH THIRD-PARTY REIMBURSEMENT

Our ability to successfully sell the Company's products, if any, depends in part on the extent to which reimbursement for the cost of such products and related treatments will be available from government health administration authorities, private health coverage insurers, HMOs and other

organizations. Adequate third-party coverage may not be available to allow the Company to obtain satisfactory price levels for third-party payor reimbursements. Government and other third-party payors are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement for new therapeutic products. If adequate coverage and reimbursement levels are not provided by government and third-party payors for uses of the Company's products, the market acceptance of these products will be more difficult.

DEPENDENCE ON KEY EMPLOYEES

We are dependent on the principal members of our management and scientific staff. The loss of these employees might slow the achievement of important development goals. It is also critical to our success to recruit and retain qualified scientific personnel to perform research and development work. Although we believe we will be successful in attracting and keeping skilled and experienced scientific personnel, we may not be able to do so on acceptable terms, because of stiff competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions.

PRODUCT LIABILITY AND POTENTIAL LIMITS OF INSURANCE COVERAGE

Drugs used in clinical trials and, if approved, drugs sold on the market may expose the Company to damages claims resulting from the use of such products. Consumers, sellers or distributors of the Company's products can make these claims. We have obtained limited product liability insurance coverage. However, such coverage is becoming increasingly expensive, and we may not be able to afford to buy enough liability insurance to protect the Company against all of the product liability losses that could possibly occur.

USE OF HAZARDOUS MATERIALS

The Company's research and development activities involve the controlled use of hazardous materials, chemicals, viruses and various radioactive compounds. Although we believe that our safety procedures for handling and disposing of such materials comply with the standards prescribed by local, state and federal regulations, there is still a risk of accidental contamination or injury. If there was such an accident, the Company could be held liable for any damages that result, which could prove costly. Although we believe that we are in compliance with applicable environmental laws and regulations and currently do not expect to have to spend significant amounts of money for environmental control facilities, we may be required to do so to comply with environmental laws and regulations in the future.

VOLATILITY OF STOCK PRICE

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. The market price can be affected by many factors, including, for example, fluctuation in our operating results, announcements of technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

ANTI-TAKEOVER PROVISIONS

Our Certificate of Incorporation provides for classified terms for the members of the Board of Directors. Our Certificate also includes a provision (the "Fair Price Provision") that requires at least 66-2/3% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, 15% or more of our voting stockholders, except in cases where certain Directors approve the transaction or certain minimum price criteria and other procedural requirements are met. Our Certificate of Incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, special meetings of our stockholders may be called only by the Board of Directors, the Chairman of the Board or the President, or by any holder of 10% or more of the outstanding Common

Stock. The classified board, Fair Price Provision and other charter provisions protect the Company in 2 ways. These provisions may discourage certain types of transactions in which the stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of the

stockholders to approve transactions that they think may be in their best interests. In addition, the 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 the Company without action by the stockholders.

ITEM 2. PROPERTIES

Isis occupies approximately 132,000 square feet of laboratory and office space (including a 12,000 square foot GMP manufacturing suite) in 5 buildings located on our "campus" in Carlsbad, California. Three of these buildings are owned by the Company and, as of December 31, 1997, secure approximately $9.3 million in indebtedness of the Company. Two of the buildings are leased. We have also leased 850 sq. ft. of office space in the United Kingdom to accommodate employees supervising European clinical trials. We believe that our facilities will be adequate to meet our needs through 1998.

ITEM 3. LEGAL PROCEEDINGS

The Company is not party to any material legal proceedings.

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

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

	HIGH	LOW
1996		
First Quarter	$ 15.13	$ 10.88
Second Quarter	$ 24.75	$ 10.38
Third Quarter	$ 19.50	$ 11.75
Fourth Quarter	$ 20.50	$ 15.38
1997		
First Quarter	$ 19.88	$ 15.00
Second Quarter	$ 17.38	$ 12.88
Third Quarter	$ 18.63	$ 12.75
Fourth Quarter	$ 18.38	$ 11.00

As of January 31, 1998, there were approximately 1,422 stockholders of record of the common stock. The Company has never paid dividends and does not

anticipate paying any dividends in the foreseeable future. Under the terms of certain term loans, the Company will be restricted from paying cash dividends until the loans are fully repaid. See Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations -- Liquidity and Capital Resources."

ITEM 6. SELECTED FINANCIAL DATA (IN THOUSANDS, EXCEPT PER SHARE AMOUNTS)

	YEARS ENDED DECEMBER 31,				
	1997	1996	1995	1994	1993
STATEMENT OF OPERATIONS DATA:					
Research and development revenues	$ 32,470	$ 22,572	$ 12,966	$ 10,088	$ 10,654
Research and development expenses	55,940	45,653	33,175	26,468	25,604
Net loss	(31,066)	(26,521)	(23,712)	(18,181)	(19,062)
Basic and diluted net loss per share	(1.17)	(1.04)	(1.10)	(0.93)	(1.22)
Shares used in computing basic and diluted net loss per share	26,456	25,585	21,514	19,542	15,685

	DECEMBER 31,				
	1997	1996	1995	1994	1993
BALANCE SHEET DATA:					
Cash, cash equivalents and short-term investments	$ 86,786	$ 77,624	$ 77,407	$ 43,440	$ 54,034
Working capital	62,573	56,300	60,040	33,679	44,076
Total assets	117,881	101,305	99,569	66,643	78,814
Long-term debt and capital lease obligations, less current portion	56,452	19,864	4,714	9,295	8,847
Accumulated deficit	(154,133)	(123,067)	(96,546)	(72,834)	(54,653)
Stockholders' equity	34,852	58,385	75,850	46,019	58,459

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

Since its inception in January 1989, almost all of the Company's resources have been devoted to its research, drug discovery and drug development programs. The Company is not yet profitable and expects to continue to have operating losses for the next several years. Isis' revenue comes from collaborative research and development agreements with pharmaceutical companies, research grants and interest income. The revenue from the collaboration agreements increases the amount of research and development activity that the Company is able to fund and offsets a portion of its research and development costs. See Item 1, "Business--Collaborative Agreements." To date, Isis has not received any significant revenue from the sale of products.

RESULTS OF OPERATIONS

Years Ended December 31, 1997 and December 31, 1996

The Company's revenue from collaborative research and development agreements was $32.5 million for the year ended December 31, 1997 compared with $22.6 million in 1996, an increase of 44%. The receipt of a $5 million pre-commercial fee from CIBA Vision together with $4 million in milestone payments from Novartis caused this revenue increase. The $5 million pre-commercial fee from CIBA Vision was the first payment under the terms of a distribution agreement for fomivirsen (ISIS 2922). The $4 million in milestone payments from Novartis was related to the initiation of Phase II clinical

studies for ISIS 3521 and ISIS 5132. Interest income was $4.1 million in 1997 versus $4.0 million in 1996.

Research and development expenses rose 22% to $55.9 million in 1997 from $45.7 million in 1996. The increase in research and development expenses occurred because compounds in preclinical and clinical development are continuing to advance into more expensive stages of development. We expect that research and development expenses will continue to increase as compounds continue to advance in clinical development.

General and administrative expenses were $8.1 million for 1997 compared with $6.2 million in 1996. This increase is primarily because of expanded business development and investor relations activities and support of our increasing research and development efforts. We expect that general and administrative expenses will continue to increase in the future to support our growing research and development activities.

Isis' net loss for 1997 was $31.1 million, or $1.17 per share, compared to $26.5 million, or $1.04 per share, for 1996. We expect that operating losses will increase for several more years as research and development activities grow. Operating losses may fluctuate from quarter to quarter because of differences in the timing of revenue and expense recognition.

At December 31, 1997, Isis' net operating loss carryforward for federal income tax purposes was approximately $161.9 million. The company's research credit carryforward for federal income tax purposes was approximately $5.8 million. The company's 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 the company's net operating loss and tax credit carryforwards. However, there may or may not be additional limitations arising from any future changes in ownership that may have a material adverse impact on the Company.

Isis believes that inflation and changing prices have not had a material effect on the Company's operations to date.

Years Ended December 31, 1996, and December 31, 1995

Isis' revenue from collaborative research and development agreements was $22.6 in 1996 and $13.0 million in 1995, an increase of 74%. Revenue from collaborative agreements increased because additional preclinical and clinical development efforts were funded by the collaborations with Novartis and Boehringer Ingelheim. The Company's interest income was $4.0 million in 1996 and $3.0 million in 1995. The increase in interest income in 1996 was due to higher cash and short-term investment balances.

Research and development expenses amounted to $45.7 million in 1996 and $33.2 million in 1995. This increase in research and development expenses resulted from Isis' growing preclinical and clinical development activities.

General and administrative expenses were $6.2 million in 1996 compared with $5.4 million in 1995. This increase was due to increases in spending for staffing, recruiting and relocation in the business development and investor relations functions.

The Company's net loss was $26.5 million, or $1.04 per share, in 1996 and $23.7 million, or $1.10 per share, in 1995.

LIQUIDITY AND CAPITAL RESOURCES

Isis has financed its operations with revenue from contract research and development, through the sale of equity securities and the issuance of long-term debt. From its inception through December 31, 1997, Isis has earned approximately $105 million in revenue from contract research and development. The Company has also raised net proceeds of approximately $180 million from the

sale of equity securities since it was founded. In 1996 and 1997, Isis borrowed approximately $47.6 million under long-term debt arrangements to finance a portion of its operations.

As of December 31, 1997, Isis had cash, cash equivalents and short-term investments of $86.8 million and working capital of $62.6 million. In comparison, the Company had cash, cash equivalents and short-term investments of $77.6 million and working capital of $56.3 million as of December 31, 1996. This increase was mainly due to the receipt of $25 million from a private debt financing, $6.4 million from borrowings under a line of credit made available to the Company by Boehringer Ingelheim, and $9.0 in milestone payments and pre-commercial fees from CIBA Vision and Novartis. This increase in cash and short-term investments was offset by the amounts needed to fund operating losses, make investments in capital equipment and building improvements and to make principal payments on debt and capital lease obligations.

The agreement with Boehringer Ingelheim provides the Company with a $40 million line of credit. This line of credit is available under certain circumstances and is to be used to support the collaboration cell adhesion programs. As of December 31, 1997, the outstanding balance under this line of credit was $22.6 million. See Note 3 to the Financial Statements, "Long-term debt and commitments".

In October 1997, Isis borrowed $25 million in a private transaction. The loan must be repaid within 10 years. The loan bears interest at 14% per annum. No payments of either principal or interest are required during the first 5 years of the loan. After the first 5 years, interest must be paid quarterly until the end of the loan. No principal payments are required until the end of the loan. Because interest is deferred during the first 5 years, the principal balance will be $50 million on November 1, 2002. In conjunction with this transaction, Isis issued warrants to purchase 500,000 shares of common stock at a price of $25 per share. The warrants will expire on November 1, 2004. The warrants have been valued at

$3.8 million. This amount has been credited to equity. See Note 3 to the Financial Statements, "Long-term debt and commitments".

As of December 31, 1997, the Company's long-term debt and capital lease obligations totaled $58.7 million compared to $26.1 million at December 31, 1996. This increase was due to the $25 million private debt financing together with the $6.4 million borrowing under the Boehringer Ingelheim line of credit and additional capital lease financing. In addition, 2 new term loans totaling $9.7 million were obtained from a bank to refinance $6.5 million in existing notes secured by the Company's real property. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for the Company's growing business. We will continue to use lease lines as long as the terms continue to remain commercially attractive. We believe that the company's existing cash, cash equivalents and short-term investments, combined with interest income and contract revenue will be sufficient to meet its anticipated requirements for at least 2 years.

YEAR 2000 COMPUTER ISSUES

Until recently many computer programs were written to store only 2 digits of date-related information. Thus the programs were unable to distinguish between the year 1900 and the year 2000. As a result, many computer experts have significant concerns regarding how those programs will function after December 31, 1999. This is frequently referred to as the "Year 2000 Problem." The Company is in the process of reviewing its computer systems to assess the potential exposure to this problem. Because Isis was founded in 1989 and all of its computer systems have been purchased or upgraded since that time, we believe the risk of material disruption to the Company's operations as a result the presence of this defect in its own computer systems is minimal.

The Company has also initiated discussions with its significant suppliers, corporate partners and financial institutions to ensure that those

parties have appropriate plans to address Year 2000 issues where their systems could impact Isis' operations. The Company is assessing the extent to which its operations are vulnerable should those organizations fail to properly modify their computer systems.

A team of Isis employees is conducting the Company's Year 2000 initiative. The team's activities are designed to ensure that there is no adverse effect on the Company's core business operations and that transactions with customers, suppliers, corporate partners and financial institutions are fully supported. These efforts are scheduled to be completed by early 1999. While the Company believes its planning and preparations will be adequate to address its Year 2000 concerns, there can be no guarantee that the systems of other companies on which the Company's systems and operations rely will be converted on a timely basis and will not have a material effect on the Company. The cost of the Year 2000 initiatives is not expected to be material to the Company's results of operations or financial position.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

The financial statements and supplementary data of the Company required by this item are filed as exhibits hereto, are listed under Item 14(a)(1) and (2), and are incorporated herein by reference.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

Not applicable.

PART III

ITEM 10. DIRECTORS AND EXECUTIVE OFFICERS

The information required by this item (with respect to Directors) is incorporated by reference from the information under the caption "Election of Directors" contained in the Company's definitive Proxy Statement (the "Proxy Statement") which will be filed on or before April 13, 1998 with the Securities and Exchange Commission in connection with the solicitation of proxies for the Company's 1998 Annual Meeting of stockholders to be held on May 22, 1998.

The required information concerning Executive Officers of the Company is contained in Item 1, Part I of this Report.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this item is incorporated by reference to the information under the caption "Executive Compensation" contained in the Proxy Statement.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

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

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS

The information required by this item is incorporated by reference to the information under the caption "Compensation Committee Interlocks and Insider Participation" and "Certain Transactions" contained in the Proxy Statement.

PART IV

ITEM 14. EXHIBITS, FINANCIAL STATEMENT SCHEDULES, AND REPORTS ON FORM 8-K

(a)(1) Index to Financial Statements

The financial statements required by this item are submitted in a separate section beginning on page 32 of this Report.

29

(A)(2) INDEX TO FINANCIAL STATEMENT SCHEDULES

None required.

(A)(3) INDEX TO EXHIBITS

See Index to Exhibits on pages 30 through 31.

The following management compensatory plans and arrangements are required to be filed as exhibits to this Report pursuant to Item 14(c):

EXHIBIT NUMBER		DESCRIPTION
10.2	--	Registrant's 1989 Stock Option Plan, as amended (the "Plan").
10.3	--	Revised form of Incentive Stock Option Agreement under the Plan. (1)
10.4	--	Revised form of Supplemental Stock Option Agreement under the Plan. (1)
10.5	--	Form of Incentive Stock Option Agreement entered into between Registrant and certain of its officers together with related schedule. (2)
10.6	--	Form of Supplemental Stock Option Agreement entered into between Registrant and certain of its officers together with related schedule. (2)
10.7	--	Registrant's 1992 Non-employee Directors Stock Option Plan, as amended. (1)
10.8	--	Revised form of Supplemental Stock Option Agreement under Registrant's 1992 Non-employee Directors' Stock Option Plan, as amended. (5)
10.9	--	Registrant's Employee Stock Purchase Plan. (3)
10.11	--	Stock Option Agreement with Daniel L. Kisner, dated as of November 29, 1990. (4)

(1) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter September 30, 1996 and incorporated herein by reference.
(2) Filed as an exhibit to Registrant's Annual Report on Form 10-K for the year ended December 31, 1994 and incorporated herein by reference.
(3) Filed as an exhibit to the Registrant's Registration Statement on Form S-8 (No. 33-42970) and incorporated herein by reference.
(4) 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.
(5) Filed as an exhibit to Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1997 and incorporated herein by reference.

(B) REPORTS ON FORM 8-K

There were no reports on Form 8-K filed by the Registrant during the fourth quarter of the fiscal year ended December 31, 1997.

(C) EXHIBITS

The exhibits required by this Item are listed under Item 14(a)(3).

(D) FINANCIAL STATEMENT SCHEDULES

The financial statement schedules required by this Item are listed under Item 14(a)(2).

SIGNATURES

Pursuant to the requirements of Section 14 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 17th day of March, 1998.

ISIS PHARMACEUTICALS, INC.

By: /s/ STANLEY T. CROOKE, M.D., Ph.D.
Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board 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 appoint Stanley T. Crooke, Daniel L. Kisner, 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 connections 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, M.D., PH.D. Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, Chief Executive Officer and Director (Principal executive officer)	March 17, 1998
/s/ B. LYNNE PARSHALL B. Lynne Parshall	Executive Vice President and Chief Financial Officer (Principal financial and accounting officer)	March 17, 1998
/s/ DANIEL L. KISNER, M.D. Daniel L. Kisner, M.D.	President, Chief Operating Officer and Director	March 17, 1998
/s/ BURKHARD BLANK Burkhard Blank	Director	March 17, 1998

/s/ CHRISTOPHER F. O. GABRIELI Christopher F. O. Gabrieli	Director	March 17, 1998
/s/ ALAN C. MENDELSON Alan C. Mendelson	Director	March 17, 1998

SIGNATURES	TITLE	DATE
/s/ WILLIAM R. MILLER William R. Miller	Director	March 17, 1998
/s/ MARK B. SKALETSKY Mark B. Skaletsky	Director	March 17, 1998
/s/ LARRY SOLL Larry Soll	Director	March 17, 1998
/s/ JOSEPH H. WENDER Joseph H. Wender	Director	March 17, 1998

INDEX TO EXHIBITS

EXHIBIT NUMBER		DESCRIPTION OF DOCUMENT
3.1	--	Amended and Restated Certificate of Incorporation. (1)
3.2	--	Bylaws. (1)
4.1	--	Reference is made to Exhibits 3.1, 3.2 and 10.19.
4.2	--	Ciba-Geigy Investor Rights Agreement between the Registrant and Novartis AG, formerly Ciba-Geigy Limited ("Novartis"), dated November 9, 1990. (1)
4.3	--	Voting Rights Agreement among the Registrant, Novartis and Dr. Crooke, dated November 9, 1990. (1)
4.4	--	Specimen stock certificate. (1)
9.1	--	Reference is made to Exhibit 4.4.
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.
10.3	--	Revised form of Incentive Stock Option Agreement under the Plan. (8)
10.4	--	Revised form of Supplemental Stock Option Agreement under the Plan. (8)
10.5	--	Form of Incentive Stock Option Agreement entered into between Registrant and certain of its officers together with related schedule. (4)
10.6	--	Form of Supplemental Stock Option Agreement entered into between Registrant and certain of its officers together with related schedule. (4)
10.7	--	Registrant's 1992 Non-Employee Directors Stock Option Plan, as amended. (8)
10.8	--	Revised form of Supplemental Stock Option Agreement under Registrant's 1992 Non-Employee Directors' Stock Option Plan. (9)
10.9	--	Registrant's Employee Stock Purchase Plan. (2)
10.10	--	Form of Employee Assignment of Patent Rights. (1)
10.11	--	Stock Option Agreement with Daniel L. Kisner, dated as of November 29, 1990. (1)
10.12	--	Amended and Restated Research, Development and Licensing Agreement by and between Isis Pharmaceuticals, Inc. and Novartis AG dated February 13, 1996 (with certain confidential information deleted). (7)
10.13	--	License Agreement between the Registrant and the PNA Group dated as of January 29, 1992 (with certain confidential information deleted). (3)
10.14	--	Stock Purchase Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted). (5)
10.15	--	Collaborative Agreement between the Registrant and Boehringer Ingelheim International GmbH, dated as of July 18, 1995 (with certain confidential information deleted).(6)
10.16	--	Agreement between Registrant and CIBA Vision Corporation dated July 10, 1997 (with certain confidential information deleted). (9)
10.17	--	Imperial Bank Note Secured by Deed of Trust dated March 24, 1997 in the amount of $6,000,000; together with the related Deed of Trust and Assignment of Rents dated March 24, 1997. (9)
10.18	--	Imperial Bank Note Secured by Deed of Trust dated March 24, 1997 in the amount of $3,706,620; together with the related Deed of Trust and Assignment of Rents dated March 24, 1997. (9)

10.19 -- Purchase Agreement for 14% Senior Subordinated Discount Notes due November 1, 2007 and Warrants for Common Stock dated October 24, 1997 (with certain confidential information deleted).

EXHIBIT NUMBER		DESCRIPTION OF DOCUMENT
10.20	--	Asset Purchase Agreement between Registrant and Gen-Probe Incorporated dated December 19, 1997 (with certain confidential information deleted).
23.1	--	Consent of Ernst & Young LLP.
24.1	--	Power of Attorney. Reference is made to page 33.
27.1	--	Financial Data Schedule.

(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 the Registrant's Registration Statement on Form S-8 (No. 33-42970) and incorporated herein by reference.

(3) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 1992 and incorporated herein by reference.

(4) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1994 and incorporated herein by reference.

(5) Filed as an exhibit to the Registrant's Report on Form 8-K dated July 18, 1995 and incorporated herein by reference.

(6) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended September 30, 1995 and incorporated herein by reference.

(7) Filed as an exhibit to the Registrant's Annual Report on Form 10-K for the year ended December 31, 1995 and incorporated herein by reference.

(8) 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.

(9) Filed as an exhibit to the Registrant's Quarterly Report on Form 10-Q for the quarter ended June 30, 1997 and incorporated herein by reference.

REPORT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

The Board of Directors
Isis Pharmaceuticals, Inc.

We have audited the accompanying balance sheets of Isis Pharmaceuticals, Inc. as of December 31, 1997 and 1996, and the related statements of operations, stockholders' equity, and cash flows for each of the

3 years in the period ended December 31, 1997. 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 generally accepted auditing standards. 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 financial statements referred to above present fairly, in all material respects, the financial position of Isis Pharmaceuticals, Inc. at December 31, 1997 and 1996, and the results of its operations and cash flows for each of the 3 years in the period ended December 31, 1997, in conformity with generally accepted accounting principles.

ERNST & YOUNG LLP

San Diego, California
January 23, 1998, except for the first
paragraph of Note 4, as to which
the date is February 27, 1998

ISIS PHARMACEUTICALS, INC.

BALANCE SHEETS
(IN THOUSANDS, EXCEPT SHARE DATA)

ASSETS

	DECEMBER 31,	
	1997	1996
Current assets:		
Cash and cash equivalents	$ 38,102	$ 37,082
Short-term investments	48,684	40,542
Prepaid expenses and other current assets	2,364	1,732
Total current assets	89,150	79,356
Property, plant and equipment, net	18,785	15,334
Patent costs, net	7,485	6,157
Deposits and other assets	2,461	458
	$ 117,881	$ 101,305

LIABILITIES AND STOCKHOLDERS' EQUITY

Current liabilities:		
Accounts payable	$ 2,843	$ 2,362
Accrued payroll and related expenses	2,242	1,489
Accrued liabilities	4,347	2,763
Deferred contract revenues	14,893	10,204
Current portion of long-term debt and capital lease obligations	2,252	6,238
Total current liabilities	26,577	23,056
Long-term debt and capital lease obligations, less current portion	56,452	19,864

Commitments (See Note 3)

Stockholders' equity:		
Common stock, $.001 par value; 50,000,000 shares authorized, 26,655,000 shares and 26,201,000 shares issued and outstanding at December 31, 1997 and 1996, respectively	27	26
Additional paid-in capital	188,793	181,248
Unrealized gain on investments	165	178
Accumulated deficit	(154,133)	(123,067)
Total stockholders' equity	34,852	58,385
	$ 117,881	$ 101,305

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF OPERATIONS
(IN THOUSANDS, EXCEPT FOR PER SHARE AMOUNTS)

	YEAR ENDED DECEMBER 31,		
	1997	1996	1995
Revenues:			
Research and development revenues under collaborative agreements	$ 32,470	$ 22,572	$ 12,966
Interest income	4,067	4,012	3,001
	36,537	26,584	15,967
Expenses:			
Research and development	55,940	45,653	33,175
General and administrative	8,078	6,246	5,402
Interest expense	3,585	1,206	1,102
	67,603	53,105	39,679
Net loss	$(31,066)	$(26,521)	$(23,712)
Basic and diluted net loss per share	$ (1.17)	$ (1.04)	$ (1.10)
Shares used in computing basic and diluted net loss per share	26,456	25,585	21,514

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF STOCKHOLDERS' EQUITY
(IN THOUSANDS)

DESCRIPTION	COMMON STOCK SHARES	COMMON STOCK AMOUNT	ADDITIONAL PAID IN CAPITAL	UNREALIZED GAINS AND (LOSSES)	ACCUMULATED DEFICIT	TOTAL STOCKHOLDERS' EQUITY
Balance at December 31, 1994	19,716	$ 20	$ 118,833	$--	$ (72,834)	$ 46,019
Options exercised and employee stock purchase plan	318	--	1,702	--	--	1,702
Issuances of common stock net of repurchases and offering costs	5,215	5	51,655	--	--	51,660
Compensation relating to the granting of options	--	--	63	--	--	63
Change in unrealized gains, net of income taxes	--	--	--	118	--	118
Net loss	--	--	--	--	(23,712)	(23,712)
Balance at December 31, 1995	25,249	25	172,253	118	(96,546)	75,850
Options exercised and employee stock purchase plan	543	1	3,164	--	--	3,165
Issuances of common stock net of repurchases and offering costs	409	--	5,822	--	--	5,822
Compensation relating to the granting of options	--	--	9	--	--	9
Change in unrealized gains, net of income taxes	--	--	--	60	--	60
Net loss	--	--	--	--	(26,521)	(26,521)
Balance at December 31, 1996	26,201	26	181,248	178	(123,067)	58,385
Options exercised and employee stock purchase plan	454	1	3,306	--	--	3,307
Issuance of warrants to purchase common stock	--	--	3,780	--	--	3,780
Compensation relating to the granting of options	--	--	459	--	--	459
Change in unrealized gains, net of income taxes	--	--	--	(13)	--	(13)
Net loss	--	--	--	--	(31,066)	(31,066)
Balance at December 31, 1997	26,655	$ 27	$ 188,793	$ 165	$(154,133)	$ 34,852

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

STATEMENTS OF CASH FLOWS
(IN THOUSANDS)

	YEAR ENDED DECEMBER 31, 1997	1996	1995
Operating activities:			
Net loss	$(31,066)	$(26,521)	$(23,712)
Adjustments to reconcile net loss to net cash provided from (used in) operating activities:			
Depreciation and amortization	3,178	2,633	2,814

Issuance of securities in exchange for technology	--	--	733
Compensation related to grant of options and stock bonus	459	9	63
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(632)	(94)	(70)
Accounts payable	481	1,365	(533)
Accrued payroll and related expenses	753	240	309
Accrued liabilities	1,584	(75)	784
Deferred contract revenues	4,689	1,291	4,532
Net cash used in operating activities	(20,554)	(21,152)	(15,080)
Investing activities:			
Short-term investments	(8,142)	(9,598)	(430)
Unrealized gain on investments	(13)	60	118
Property, plant and equipment	(3,454)	(862)	(1,073)
Patent costs	(1,455)	(1,439)	(742)
Deposits and other assets	(2,098)	568	629
Net cash used in investing activities	(15,162)	(11,271)	(1,498)
Financing activities:			
Net proceeds from issuance of equity	7,087	8,987	52,629
Proceeds from long-term borrowing	33,320	16,200	--
Principal payments on debt and capital lease obligations	(3,671)	(2,145)	(2,514)
Net cash provided from financing activities	36,736	23,042	50,115
Net increase (decrease) in cash and cash equivalents	1,020	(9,381)	33,537
Cash and cash equivalents at beginning of year	37,082	46,463	12,926
Cash and cash equivalents at end of year	$ 38,102	$ 37,082	$ 46,463
Supplemental disclosures of cash flow information:			
Interest paid	$ 2,644	$ 1,150	$ 1,094
Supplemental disclosures of non-cash investing and financing activities:			
Additions to debt and capital lease obligations for acquisitions of property, plant and equipment	$ 2,953	$ 2,325	$ 517

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS
DECEMBER 31, 1997

1. ORGANIZATION AND SIGNIFICANT ACCOUNTING POLICIES

Organization and business activity--Isis Pharmaceuticals was incorporated in California on January 10, 1989. In conjunction with its initial public offering the Company was reorganized as a Delaware corporation, as Isis Pharmaceuticals, Inc., in April 1991. The Company was organized principally to develop human therapeutic drugs using antisense and combinatorial technology.

Basic net loss per share--In 1997, the Financial Accounting Standards Board issued Statement No. 128, "Earnings Per Share." Statement No. 128 replaced the calculation of primary and fully diluted earnings per share with basic and diluted earnings per share. Basic earnings per share excludes any dilutive effects of options, warrants and convertible securities. Dilutive earnings per share includes the dilutive effects of options, warrants and convertible securities. Options and warrants to purchase common stock were not included in the computation of diluted net loss per share because the effect

would be antidilutive. All net losses per share have been presented to conform to Statement No. 128 requirements.

Contract revenues and expenses--Contract revenues are recorded as earned based on the performance requirements of the collaborative research and development contracts. Payments received in excess of amounts earned are recorded as deferred contract revenues. Research and development costs are expensed as incurred. For the years ended December 31, 1997, 1996 and 1995, costs and expenses of approximately $31,000,000, $29,000,000, and $18,100,000 respectively, were related to collaborative research and development arrangements.

Cash equivalents and short-term investments--Cash equivalents and short-term investments consist of highly liquid debt instruments. The Company considers instruments with original maturities of less than 90 days to be cash equivalents. The Company has recorded its cash equivalents and short-term investments at fair market value as of December 31, 1997, and has classified all of its investments as available- for-sale. This category includes all securities which the Company does not have the positive intent and ability to hold to maturity. The measurement basis for available-for-sale securities is fair market value. Unrealized gains and losses, net of the related tax effect, are included as a separate component of stockholders' equity. See Note 2 - Investments.

Property, plant and equipment--Property, plant and equipment is stated at cost and consists of the following (in thousands):

	DECEMBER 31,	
	1997	1996
Land	$ 1,163	$ 1,163
Buildings and improvements	13,607	12,974
Equipment	21,599	16,311
Furniture and fixtures	927	441
	37,296	30,889
Less accumulated depreciation	(18,511)	(15,555)
	$ 18,785	$ 15,334

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

Building	31.5 years
Improvements	15 years
Equipment	2.5-5 years
Furniture and fixtures	5 years

Patent costs--The Company capitalizes certain costs related to patent applications. Accumulated costs are amortized over the estimated economic lives of the patents using the straight-line method, beginning with the date the patents are issued. Accumulated amortization was $240,000 at December 31, 1997 and $112,000 at December 31, 1996.

Use of estimates--The preparation of financial statements in conformity with generally accepted accounting principles requires management to make

estimates and assumptions that affect the amounts reported in the financial statements and accompanying notes. Actual results could differ from those estimates.

2. INVESTMENTS

The Company invests its excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. The Company has established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends in yields and interest rates. The Company has not experienced any losses on its short-term investments. As of December 31, 1997, 77% of the debt securities held by the Company had a contractual maturity of one year or less, and the remaining 23% of the portfolio was due within 2.5 years.

The following is a summary of available-for-sale securities:

	AVAILABLE-FOR-SALE SECURITIES		
	COST	GROSS UNREALIZED GAINS	ESTIMATED FAIR VALUE
DECEMBER 31, 1997	(in thousands)		
U.S. Treasury securities and obligations of U.S. Government agencies	$32,980	$ 105	$33,085
U.S. corporate debt securities	15,539	60	15,599
Total debt securities	$48,519	$ 165	$48,684
DECEMBER 31, 1996			
U.S. Treasury securities and obligations of U.S. Government agencies	$36,416	$ 165	$36,581
U.S. corporate debt securities	3,948	13	3,961
Total debt securities	$40,364	$ 178	$40,542

3. LONG-TERM DEBT AND COMMITMENTS

In 1997, the Company obtained $25,060,000 in private debt financing. The terms of the financing provide for a 10 year maturity on the debt, interest of 14% per annum and deferred interest payments for the first 5 years of the loan. After the first 5 years, interest must be paid quarterly until the end of the loan. No principal repayments are required until the end of the loan. Because interest is deferred during the first 5 years, the principal balance will be $50 million on November 1, 2002. In conjunction with the debt financing, Isis has issued warrants to the lender to purchase 500,000 shares of common stock, exercisable at $25 per share. The warrants have been valued at $3,780,000 and have been credited to equity. The debt is carried on the balance sheet net of the amortized amount allocated to the warrants, and including accrued interest. The carrying amount at December 31, 1997 was $21,935,000.

In 1997, the Company obtained 2 new term loans from a bank to refinance existing notes secured by real property and to fund facilities expansion. Both notes are secured by the Company's real property and bear interest at the prime interest rate plus 0.5%. The first note in the amount of $3,707,000 requires monthly principal repayments of $12,433 plus interest with the remaining principal balance due in April 2002. The balance of the note at December 31, 1997 was $3,588,000. The second note in the amount of $6,000,000 requires monthly principal repayments of $50,000 plus related interest with the remaining principal balance due in July 2002. The balance at December 31, 1997 was $5,700,000.

In 1996, The Company borrowed $16,200,000 under a $40,000,000 line of credit made available under the terms of its collaborative agreement with Boehringer Ingelheim International GmbH. In 1997, an additional $6,376,000 was borrowed. The borrowed funds are being used to fund research and development costs associated with the collaboration. Borrowings under the line of credit bear interest at the 7 year U.S. interbanking rate plus 2.0%, determined at the time each advance is made. Interest payments are due twice each year with principal repayment due 7 years after the advance date. The principal may be repaid in cash or stock, at the Company's option. If the Company elects to repay the loan in shares of Isis common stock, repayment will be made at a share price equal to 90% of the average market value over the 20 trading days preceding the maturity date. The balance under this line of credit as of December 31, 1997 was $22,576,000.

The Company leases equipment and certain office and lab space under non-cancelable operating and capital leases with terms through February 2007. Annual future minimum payments under operating and capital leases and future maturities of long-term debt as of December 31, 1997 are as follows (in thousands):

	OPERATING LEASES	CAPITAL LEASES	LONG-TERM DEBT
1998	$ 1,150	$ 1,910	$ 3,456
1999	990	1,575	3,388
2000	751	1,247	3,321
2001	743	1,060	3,253
2002	689	--	8,447
Thereafter	715	--	70,905
Total minimum payments	$ 5,038	5,792	92,770

Less amount representing interest	(887)	(38,971)
Present value of future minimum payments	4,905	53,799
Less current portion	(1,503)	(749)
Total	$ 3,402	$ 53,050

Rent expense for the years ended December 31, 1997, 1996, and 1995 was $1,030,000, $520,000 and $303,000, respectively. Cost of equipment under capital leases at December 31, 1997 and 1996 was $14,133,000 and $12,781,000, respectively. Accumulated depreciation of equipment under capital leases at December 31, 1997 and 1996 was $11,177,000 and $9,899,000, respectively.

4. STOCKHOLDERS' EQUITY

Stock Option Plans and Other Employee Option Grants--In June 1989, the Company adopted a stock option plan which provides for the issuance of incentive and non-qualified stock options for the purchase of up to 10,200,000 shares of common stock (2,000,000 shares of which remain subject to stockholders' approval) to its employees and certain other individuals. In addition to the options issued under the terms of the 1989 plan, non-qualified options to purchase 319,000 shares of common stock have been granted to certain employees. The plan also includes provisions for the issuance of stock pursuant to restricted stock purchases and bonuses. Typically options expire 10 years from the date of grant. Options granted after December 31, 1995 vest over a 4 year period, with 25% exercisable at the end of 1 year from the date of the grant and the balance vesting ratably thereafter. Options granted before January 1, 1996 generally vest over a 5 year period. At December 31, 1997, a total of 3,377,000 shares

were exercisable, with an aggregate exercise price of $26,585,000. As of that date, 8,200,000 shares had been reserved for issuance under the 1989 plan, of which 704,000 were available for future grant.

In July 1992, the Company adopted the 1992 Non-Employee Directors' Stock Option Plan which provides for the issuance of non-qualified stock options for the purchase of up to 300,000 shares of common stock to its non-employee directors. Options under this plan expire 10 years from the date of grant. Options granted after December 31, 1995 become exercisable in 4 equal annual installments beginning 1 year after the date of grant. Options granted before January 1, 1996 vest over a 5 year period. At December 31, 1997, 99,000 shares issued under this plan were exercisable and 68,000 Shares were available for future grant.

The following table summarizes stock option activity for the years ended December 31, 1997 and 1996 (in thousands, except per share data):

	NUMBER OF SHARES	PRICE PER SHARE		
Outstanding at December 31, 1995	5,446	$ .14	to	$ 19.75
Granted	1,337	11.38	to	20.00
Exercised	(468)	.14	to	17.88
Terminated	(222)	4.00	to	18.63
Outstanding at December 31, 1996	6,093	.14	to	20.00

Granted	1,071	13.19	to	19.88
Exercised	(395)	.14	to	16.00
Terminated	(327)	3.75	to	18.25
Outstanding at December 31, 1997	6,442	.14	to	20.00

The following table summarizes information concerning currently outstanding and exercisable options (in thousands, except contractual life and exercise price data):

	OPTIONS OUTSTANDING			OPTIONS EXERCISABLE	
RANGE OF EXERCISE PRICE	NUMBER OUTSTANDING AS OF 12/31/97	WEIGHTED AVERAGE REMAINING CONTRACTUAL LIFE	WEIGHTED AVERAGE EXERCISE PRICE	NUMBER EXERCISABLE AS OF 12/31/97	WEIGHTED AVERAGE EXERCISE PRICE
$0.14 - $5.00	1,204	5.40	$3.29	745	$2.82
$5.13 - $6.75	1,364	5.75	$6.18	1,051	$6.17
$6.81 - $11.13	1,081	5.58	$8.66	814	$8.55
$11.25 - $13.13	1,275	7.88	$12.74	590	$12.74
$13.18 - $18.00	1,303	8.56	$16.20	212	$14.91
$18.13 - $20.00	215	8.60	$18.57	63	$18.43
$0.14 - $20.00	6,442	6.74	$9.80	3,476	$7.89

Employee Stock Purchase Plan--In 1991, the Board of Directors adopted the Employee Stock Purchase Plan and reserved 500,000 shares of common stock for issuance thereunder. 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 offer or the end of each six-month purchase period. During 1997, 58,000 shares were issued to employees at prices ranging from $10.73 to $15.30 per share. In 1996, 75,000 shares were issued at prices ranging from $3.40 to $11.16 per share. At December 31, 1997, 184,000 shares were available for purchase under this plan.

Stock-Based Employee Compensation--The Company has adopted the disclosure-only provision of Statement of Financial Accounting Standards No. 123, "Accounting for Stock-Based Compensation." Accordingly, no compensation expense has been recognized for the stock option plans. Had compensation expense been determined consistent with Statement No. 123, the Company's net loss and basic net loss per share would have been changed to the following pro forma amounts (in thousands, except per share amounts):

	1997	1996
Net loss - as reported	$ (31,066)	$ (26,521)
Net loss - pro forma	(38,004)	(32,200)
Basic net loss per share - as reported	$ (1.17)	$ (1.04)
Basic net loss per share - pro forma	(1.44)	(1.26)

The fair value of each option grant is estimated on the date of grant using the Black-Scholes option pricing model with the following weighted- average assumptions for both 1996 and 1997: expected life of 1 year from vesting date for regular employees, 2 years from vesting date for Directors and Vice Presidents, and 4 years from vesting date for Executive Officers; expected dividend yield of zero percent and expected volatility of 60 percent. Risk-free interest rate was based on the Treasury Bill rate at the end of each quarter during 1996 and 1997. All options granted during the quarter were valued using the same risk-free rate for the quarter. The weighted average fair value of options granted was $7.20 for 1996 and $8.50 for 1997.

Warrants--In 1993, the Company issued Class A warrants in connection with a strategic alliance with PerSeptive Biosystems, Inc. As of December 31, 1997, 448,001 of the warrants remain outstanding at an exercise price of $7.75 per share. The warrants expire March 15, 1999.

In 1997, Isis issued 500,000 warrants in conjunction with a private debt financing agreement. As of December 31, 1997, all of the warrants remain outstanding at an exercise price of $25 per share. The warrants expire November 1, 2004. See Note 3.

As of December 31, 1997, total common shares reserved for future issuance was 10,363,000 (2,000,000 shares of which remain subject to stockholders' approval).

5. INCOME TAXES

Significant components of the Company's deferred tax assets as of December 31, 1997 and 1996 are shown below. Valuation allowances of $71,400,000 and $55,313,000 have been recognized for 1997 and 1996, respectively, to offset the net deferred tax assets as realization of such assets is uncertain.

	1997	1996
Deferred tax assets:		
Capitalized research expense	$ 7,741,000	$ 6,287,000
Net operating loss carryforwards	57,959,000	42,136,000
Research and development credits	7,258,000	5,683,000
Other, net	889,000	3,131,000
Total deferred tax assets	73,847,000	57,237,000
Deferred tax liabilities:		
Patent expense	(2,447,000)	(1,924,000)
Total deferred tax liabilities	(2,447,000)	(1,924,000)
Total net deferred tax assets	71,400,000	55,313,000
Valuation allowance for deferred tax assets	(71,400,000)	(55,313,000)
Net deferred tax assets	$ 0	$ 0

At December 31, 1997, approximately $2,880,000 of the valuation allowance for deferred tax assets relates to stock option deductions which, when recognized, will be allocated directly to additional paid-in capital.

At December 31, 1997, the Company had federal and California tax net operating loss carryforwards of approximately $161,884,000, and $22,606,000, respectively. The Company also had federal and California research credit carryforwards of approximately $5,760,000 and $2,305,000, respectively. The difference between the tax loss carryforwards for federal and California purposes was attributable to the capitalization of research and development expenses for California tax purposes and a required 50% limitation in the utilization of California loss carryforwards. The federal tax loss carryforward and the research credit carryforwards will begin expiring in 2004 unless previously utilized. Approximately $3,000,000 of the California tax loss carryforward expired during 1997 and the related deferred tax asset and tax loss carryforward amounts have been reduced accordingly. The remaining California tax loss carryforward will begin expiring in 1998, unless utilized.

Annual use of the Company's net operating loss and credit carryforwards will be limited under the Internal Revenue Code as a result of cumulative changes in ownership of more than 50% during the periods ended December 31, 1989 and 1991. However, the Company believes that such limitations will not have a material impact upon the utilization of the carryforwards.

6. RESEARCH AND DEVELOPMENT COLLABORATIVE ARRANGEMENTS

In 1990, Isis entered into a collaborative agreement with Novartis to discover and investigate oligonucleotide compounds active against 4 specific targets In 1996, Isis and Novartis signed a definitive agreement broadening the companies' antisense research and development collaboration to include the development of ISIS 3521 and ISIS 5132, anticancer compounds that were discovered through the research collaboration. The broadened collaboration also includes research to discover additional therapeutic compounds. Under the terms of the expanded collaboration, Novartis is funding the development of both ISIS 3521 and ISIS 5132. Isis receives certain milestone payments from Novartis as these compounds and subsequent compounds arising out of the expanded research program progress through development. Novartis will market these compounds worldwide and will pay Isis a royalty based on sales. Included in the statement of operations for the years ended December 31, 1997, 1996 and 1995 are contract revenues arising from this collaboration totaling $21,106,000, $14,003,000 and $7,308,000, respectively.

As part of the expanded collaborative relationship, Novartis also made additional equity investments in Isis totaling $10,000,000 in 1995. In June 1995, Novartis made a private equity investment purchasing 200,000 shares for $3,000,000. In October 1995, Novartis purchased an additional 700,000 shares for $7,000,000 as part of the Company's public offering. As of December 31, 1997, Novartis owned approximately 8% of the outstanding common stock of the Company.

In December 1990, the Company entered into an agreement for a collaborative research program with Eisai Co., Ltd. ("Eisai") to discover and investigate oligonucleotide compounds active against CMV. As a result of the collaboration efforts under this program, in December 1992, the Company entered into a co-development agreement with Eisai to develop a specific oligonucleotide compound (ISIS 2922) for North American and European markets. In August 1996, Isis reacquired full ownership of ISIS 2922 in exchange for a royalty on future sales. Included in the statement of operations are co-development revenues of $3,788,000 and $2,720,000 for the years ended December 31, 1996 and 1995, respectively.

In July 1997, the Company and CIBA Vision Corporation ("CIBA Vision") entered into an agreement granting CIBA Vision exclusive worldwide distribution

rights for fomivirsen (ISIS 2922). Under the terms of the agreement, Isis will receive $20 million in pre-commercial fees and milestones payments through the time of regulatory approval in the United States and Europe. Isis will manufacture and sell fomivirsen to CIBA Vision at a price that will allow Isis and CIBA Vision to share the commercial value of the product. CIBA Vision will market and sell fomivirsen worldwide and will be responsible for regulatory approvals outside of the United States and Europe. If regulatory approvals are obtained, CIBA Vision will hold the registrations. Additionally, CIBA Vision received the option to acquire the exclusive license to market and distribute a second generation antisense compound to treat CMV retinitis (ISIS 13312) which is currently in development by Isis. Included in the statement of operations for the year ended December 31, 1997 are contract revenues of $5,000,000 from this arrangement.

In July 1995, the Company and Boehringer Ingelheim International GmbH ("Boehringer Ingelheim") signed definitive agreements and completed the formation of a major collaboration in cell adhesion drug design, discovery, development and commercialization. Boehringer Ingelheim purchased 2,000,000 shares of common stock for $28,500,000 in cash plus certain license rights. Of the $28,500,000, $21,300,000 was accounted for as equity and $7,200,000 was accounted for as deferred revenue,

representing Boehringer Ingelheim's advance payment of research and development costs under the collaboration. In December 1996, coinciding with the achievement of a milestone, Boehringer Ingelheim purchased 409,000 shares for $10,000,000. Of that total, $6,000,000 was accounted for as equity and $4,000,000 as deferred revenue. The agreement also provides that Boehringer Ingelheim is entitled to designate 1 person for election to Isis' Board of Directors. As of December 31, 1997 Boehringer Ingelheim owns approximately 9% of the outstanding common stock of the Company. Boehringer Ingelheim and Isis are providing equal funding for the combined research and development program and will share equally in the profits from all products of the collaboration. Boehringer Ingelheim has also provided Isis with a $40,000,000 line of credit, available under certain circumstances to be used in support of the combined programs. As of December 31, 1997, the outstanding balance under this line of credit was $22,576,000. The statement of operations for the years ended December 31, 1997, 1996 and 1995 reflects contract revenues of $5,603,000, $4,024,000 and $1,267,000, respectively, from this collaboration.

7. EARNINGS PER SHARE

In July 1997, the Financial Accounting Standards Board issued Statement No. 128, "Earnings Per Share." The Company has adopted the provisions of the new standard. In accordance with the statement, prior periods have not been restated as the effect of the change is not material.

The following table sets forth the computation of basic and diluted earnings per share:

	YEAR ENDED DECEMBER 31,		
	1997	1996	1995
Numerator:			
Numerator for basic net loss per share-net loss	(31,066)	(26,521)	(23,712)
Numerator for diluted net loss per share-net loss	(31,066)	(26,521)	(23,712)

Denominator:			
Denominator for basic net loss per share-weighted average shares	26,456	25,585	21,514
Denominator for diluted net loss per share-weighted average shares	26,456	25,585	21,514
Basic net loss per share	(1.17)	(1.04)	(1.10)
Diluted net loss per share	(1.17)	(1.04)	(1.10)

Options and warrants to purchase common stock were not included in the computation of diluted net loss per share because the effect would be antidilutive. For additional disclosures regarding outstanding stock options and warrants, see Note 4-Stockholders' equity.

1

EXHIBIT 10.2

Registrant's 1989 Stock Option Plan, as amended.

2

ISIS PHARMACEUTICALS, INC.
1989 STOCK OPTION PLAN

As Amended September 5, 1991
As Amended September 4, 1992
As Amended January 4, 1993
As Amended December 2, 1993 and January 20, 1994
As Amended December 7, 1994
As Amended February 27, 1995 and December 14, 1995
As Amended September 6, 1996
As Amended February 27, 1998

1. PURPOSE.

(a) The purpose of the Plan is to provide a means by which selected employees and directors (if declared eligible under paragraph 4) of and consultants to Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), and its Affiliates, as defined in subparagraph 1(b), may be given an opportunity to benefit from increases in value of the stock of the Company through the granting of (i) incentive stock options, (ii) supplemental stock options, (iii) stock bonuses, and (iv) rights to purchase stock, all as defined below.

(b) The word "Affiliate" as used in the Plan means any parent corporation or subsidiary corporation of the Company, as those terms are defined in Sections 424(e) and (f), respectively, of the Internal Revenue Code of 1986, as amended (the "Code").

(c) The Company, by means of the Plan, seeks to retain the services of persons now employed by or serving as consultants or directors to the Company, to secure and retain the services of new employees/persons capable of filling such positions, and to provide incentives for such persons to exert maximum efforts for the success of the Company.

(d) The Company intends that the rights issued under the Plan ("Stock Awards") will, in the discretion of the Board of Directors of the Company (the "Board") or any committee to which responsibility for administration of the Plan has been delegated pursuant to subparagraph 2(c), be either (i) stock options granted pursuant to paragraph 5 hereof, including incentive stock options as that term is used in Section 422 of the Code ("Incentive Stock Options"), or options which do not qualify as Incentive Stock Options ("Supplemental Stock Options") (together hereinafter referred to as "Options"), or (ii) stock bonuses or rights to purchase restricted stock granted pursuant to paragraph 6 hereof. All Options will be separately designated Incentive Stock Options or Supplemental Stock Options at the time of grant, and in such form as issued pursuant to paragraph 5, and a separate certificate or certificates will be issued for

3

shares purchased on exercise of each type of Option. An Option designated as a Supplemental Stock Option will not be treated as an Incentive Stock Option.

2. ADMINISTRATION.

(a) The Plan will be administered by the Board unless and until the Board delegates administration to a committee, as provided in subparagraph 2(c).

(b) The Board will have the power, subject to, and within the limitations of, the express provisions of the Plan:

(1) To determine from time to time which of the persons eligible under the Plan will be granted Stock Awards; when and how Stock Awards will be granted; whether a Stock Award will be an Incentive Stock Option, a Supplemental Stock Option, a stock bonus, a right to purchase restricted stock, or a combination of the foregoing; the provisions of each Stock Award granted (which need not be identical), including the time or times when a person will be permitted to purchase or receive stock pursuant to a Stock Award; and the number of shares with respect to which Stock Awards will be granted to each such person.

(2) To construe and interpret the Plan and Stock Awards granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Stock Award, in a manner and to the extent it will deem necessary or expedient to make the Plan fully effective.

(3) To amend the Plan as provided in paragraph 12.

(4) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company.

(c) The Board may delegate administration of the Plan to one or more committees, each committee composed of not fewer than 2 members (each, a "Committee"). If administration is delegated to a Committee, that Committee will have, in connection with the administration of the Plan, the powers theretofore possessed by the Board, subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Board may abolish a Committee at any time and revest in the Board the administration of the Plan. Additionally, and notwithstanding anything to the contrary contained herein, the Board or Committee may delegate to a committee of one or more members of the Board the authority to grant options to certain eligible persons in accordance with guidelines approved by the Board or Committee.

3. SHARES SUBJECT TO THE PLAN.

(a) Subject to the provisions of paragraph 11 relating to adjustments upon changes in stock, the stock that may be issued pursuant to Stock Awards granted under the Plan will not exceed in the aggregate 10,200,000 shares of the Company's common stock. If any Stock Award granted under the Plan will for any reason expire or otherwise terminate without having been exercised in full, the stock not purchased under such Stock Award will again become available for the Plan.

(b) The stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

(c) An Incentive Stock Option may be granted to an eligible person under the Plan only if the aggregate fair market value (determined at the time the Option is granted) of the stock with respect to which incentive stock options (as defined in the Code) granted after 1986 are exercisable for the first time by such optionee during any calendar year under all Incentive Stock Option plans of the Company and its Affiliates does not exceed $100,000. If it is determined that an entire Option or any portion thereof does not qualify for treatment as an Incentive Stock Option by reason of exceeding such maximum, such Option or the applicable portion will be considered a Supplemental Stock Option.

4. ELIGIBILITY.

(a) Incentive Stock Options may be granted only to employees (including officers) of the Company or its Affiliates. A director of the Company will not be eligible to receive Incentive Stock Options unless such director is also an employee (including an officer) of the Company or any Affiliate. Stock Awards other than Incentive Stock Options may be granted only to employees (including officers) of, directors of or consultants to the Company or its Affiliates.

(b) No person will be eligible for the grant of an Incentive Stock Option under the Plan if, at the time of grant, such person owns (or is deemed to own pursuant to Section 424(d) of the Code) stock possessing more than 10% of the total combined voting power of all classes of stock of the Company or of any of its Affiliates unless the exercise price of such Option is at least 110% of the fair market value of such stock at the date of grant and the term of the Option does not exceed 5 years from the date of grant.

(c) No person will be eligible to be granted Options covering more than 294,873 shares of the Company's common stock in any 12 month period.

5. OPTION PROVISIONS.

Each Option will be in such form and will contain such terms and conditions as the Board or the Committee will deem appropriate. The provisions of separate Options need not be identical, but each Option will include (through incorporation of provisions hereof by reference in the Option or otherwise) the substance of each of the following provisions:

(a) No Option will be exercisable after the expiration of 10 years from the date it was granted.

(b) The exercise price of each Incentive Stock Option will be not less than 100% of the fair market value of the stock subject to the Option on the date the Option is granted. The exercise price of each Supplemental Stock Option will be not less than 85% of the fair market value of the stock subject to the Option on the date the Option is granted. Notwithstanding the foregoing, an Option (whether an Incentive Stock Option or Supplemental Stock Option) may be granted with an exercise price lower than set forth in the preceding sentences if such Option is granted pursuant to an assumption or substitution for another option in a manner satisfying the provisions of Section 424(a) of the Code.

(c) The purchase price of stock acquired pursuant to an Option will be paid, to the extent permitted by applicable statutes and regulations, either (i) in cash at the time the Option is exercised, or (ii) at the discretion of the Board or the Committee, either at the time of the grant or exercise of the Option, (A) by delivery to the Company of other common stock of the Company, (B) according to a deferred payment or other arrangement (which may include, without limiting the generality of the foregoing, the use of other common stock of the Company) with the person to whom the Option is granted or to whom the Option is transferred pursuant to subparagraph 5(d), or (C) in any other form of legal consideration that may be acceptable to the Board or the Committee.

In the case of any deferred payment arrangement, interest will be payable at least annually and will be charged at the minimum rate of interest necessary to avoid the treatment as interest, under any applicable provisions of the Code, of any amounts other than amounts stated to be interest under the deferred payment arrangement.

(d) An Incentive Option will not be transferable except by will or by the laws of descent and distribution, and will be exercisable during the lifetime of the person to whom the Option is granted only by such person. A Supplemental Stock Option may be transferable at the discretion of the Board or the Committee.

(e) The total number of shares of stock subject to an Option may, but need not, be allotted in periodic installments (which may, but need not, be equal). From time to time during each of such installment periods, the Option may become exercisable ("vest") with respect to some or all of the shares allotted to that period, and may be exercised with respect to some or all of the shares allotted to such period and/or any prior period as to which the Option was not fully exercised. During the remainder of the term of the Option (if its term extends beyond the end of the installment periods), the Option may be exercised from time to time with respect to any shares then remaining subject to the Option. The provisions of this subparagraph 5(e) are subject to any Option provisions governing the minimum number of shares as to which an Option may be exercised.

(f) The Company may require any optionee, or any person to whom an Option is transferred under subparagraph 5(d), as a condition of exercising any such Option, (1) to give written assurances satisfactory to the Company as to the optionee's knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters, and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Option; and (2) to give written assurances satisfactory to the Company stating that such person is acquiring the stock subject to the Option for such person's own account and not with any present intention of selling or otherwise distributing the stock. These requirements, and any assurances given pursuant to such requirements, will be inoperative as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws.

(g) An Option will terminate 3 months after termination of the optionee's employment or relationship as a consultant or director with the Company or an Affiliate, unless (i) such termination is due to such person's permanent and total disability, within the meaning of Section 422(c)(6) of the Code, in which case the Option may, but need not, provide that it may be exercised at any time within 1 year following such termination of employment or relationship as a consultant or director; or (ii) the optionee dies while in the employ of or while serving as a consultant or director to the Company or an Affiliate, or within not more than 3 months after termination of such relationship, in which case the Option may, but need not, provide that it may be exercised at any time within 18 months following the death of the optionee by the person or persons to whom the optionee's rights under such Option pass by will or by the laws of descent and distribution; or (iii) the Option by its terms specifies either (a) that it will terminate sooner than 3 months after termination of the optionee's employment or relationship as a consultant or director or (b) that it may be exercised more than 3 months after termination of the relationship with the Company or an Affiliate. This subparagraph 5(g) will not be construed to extend the term of any Option or to permit anyone to exercise the Option after expiration of its term, nor will it be construed to increase the number of shares as to which any Option is exercisable from the amount exercisable on the date of termination of the optionee's employment or relationship as a consultant or director.

(h) The Option may, but need not, include a provision whereby the optionee may elect at any time during the term of his or her employment or relationship as a consultant or director with the Company or any Affiliate to exercise the Option as to any part or all of the shares subject to the Option prior to the stated vesting date of the Option or of any installment or installments specified in the Option. Any shares so purchased from any unvested installment or Option may be subject to a repurchase right in favor of the Company or to any other restriction the Board or the Committee determines to be appropriate.

(i) To the extent provided by the terms of an Option, the optionee may satisfy any federal, state or local tax withholding obligation

relating to the exercise of such Option by any of the following means or by a combination of such means: (1) tendering a cash payment; (2) authorizing the Company to withhold from the shares of the common stock otherwise issuable to the participant as a result of the exercise of the Option a number of shares having a fair market value less than or equal to the amount of the withholding tax obligation; or (3) delivering to the Company owned and unencumbered shares of the common stock having a fair market value less than or equal to the amount of the withholding tax obligation.

6. TERMS OF STOCK BONUSES AND PURCHASES OF RESTRICTED STOCK.

Each stock bonus or restricted stock purchase agreement will be in such form and will contain such terms and conditions as the Board or the Committee will deem appropriate. The terms and conditions of stock bonus or restricted stock purchase agreements may change from time to time, and the terms and conditions of separate agreements need not be identical, but each stock bonus or restricted stock purchase agreement will include (through incorporation of provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions as appropriate:

(a) The purchase price under each stock purchase agreement will be such amount as the Board or Committee will determine and designate in such agreement. Notwithstanding the foregoing, the Board or the Committee may determine that eligible participants in the Plan may be awarded stock pursuant to a stock bonus agreement in consideration for past services actually rendered to the Company or for its benefit.

(b) No rights under a stock bonus or restricted stock purchase agreement will be assignable by any participant under the Plan, either voluntarily or by operation of law, except where such assignment is required by law or expressly authorized by the terms of the applicable stock bonus or restricted stock purchase agreement.

(c) The purchase price of stock acquired pursuant to a stock purchase agreement will be paid either: (i) in cash at the time of purchase; (ii) at the discretion of the Board or the Committee, according to a deferred payment or other arrangement with the person to whom the stock is sold; or (iii) in any other form of legal consideration that may be acceptable to the Board or the Committee in their discretion. Notwithstanding the foregoing, the Board or the Committee to which administration of the Plan has been delegated may award stock pursuant to a stock bonus agreement in consideration for past services actually rendered to the Company or for its benefit.

(d) Shares of stock sold or awarded under the Plan may, but need not, be subject to a repurchase option in favor of the Company in accordance with a vesting schedule to be determined by the Board or the Committee.

(e) In the event a person ceases to be an employee of or ceases to serve as a consultant to the Company or an Affiliate, the Company may repurchase or otherwise reacquire any or all of the shares of stock held by that person which have not vested as of the date of termination under the terms of the stock bonus or restricted stock purchase agreement between the Company and such person.

7. COVENANTS OF THE COMPANY.

(a) During the terms of the Stock Awards granted under the Plan, the Company will keep available at all times the number of shares of stock required to satisfy such Stock Awards.

(b) The Company will seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to issue and sell shares of stock under the Stock Awards granted under the Plan; provided, however, that this undertaking will not require the Company to register under the Securities Act either the Plan, any Stock Award granted under the Plan or any stock issued or issuable pursuant to any such Stock Award. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the

Company deems necessary for the lawful issuance and sale of stock under the Plan, the Company will be relieved from any liability for failure to issue and sell stock upon exercise of such Stock Awards unless and until such authority is obtained.

8. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of stock pursuant to Stock Awards granted under the Plan will constitute general funds of the Company.

9. MISCELLANEOUS.

(a) The Board or the Committee will have the power to accelerate the time during which a Stock Award may be exercised or the time during which a Stock Award or any part thereof will vest, notwithstanding the provisions in the Stock Award stating the time during which it may be exercised or the time during which it will vest.

(b) Neither an optionee nor any person to whom an Option is transferred under subparagraph 5(d) will be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares subject to such Option unless and until such person has satisfied all requirements for exercise of the Option pursuant to its terms.

(c) Throughout the term of any Option granted pursuant to the Plan, the Company will make available to the holder of such Option, not later than 120 days

after the close of each of the Company's fiscal years during the Option term, upon request, such financial and other information regarding the Company as comprises the annual report to the stockholders of the Company provided for in the bylaws of the Company.

(d) Nothing in the Plan or any instrument executed or Stock Award granted pursuant thereto will confer upon any eligible employee, consultant, director or holder of Stock Awards under the Plan any right to continue in the employ of the Company or any Affiliate (or to continue acting as a consultant or director) or will affect the right of the Company or any Affiliate to terminate the employment or consulting relationship or directorship of any eligible employee, consultant, director or holder of Stock Awards under the Plan with or without cause. In the event that a holder of Stock Awards is permitted or otherwise entitled to take a leave of absence, the Company will have the unilateral right to (i) determine whether such leave of absence will be treated as a termination of employment or relationship as consultant or director for purposes of paragraphs 5(g) or 6(e) hereof and corresponding provisions of any outstanding Stock Awards, and (ii) suspend or otherwise delay the time or times at which exercisability or vesting would otherwise occur with respect to any outstanding Stock Awards under the Plan.

10. CANCELLATION AND RE-GRANT OF OPTIONS.

The Board or the Committee will have the authority to effect, at any time and from time to time, with the consent of the affected optionees, (i) the repricing of any or all outstanding Options under the Plan and/or (ii) the cancellation of any or all outstanding Options under the Plan and the grant in substitution therefor of new Options under the Plan covering the same or different numbers of shares of common stock, but having an exercise price per share not less than 85% of the fair market value (100% of the fair market value in the case of an Incentive Stock Option or, in the case of a 10% stockholder (as defined in subparagraph 4(b)), not less than 110% of the fair market value) per share of common stock on the new grant date. Notwithstanding the foregoing, an Option (whether an Incentive stock Option or Supplemental Stock Option) may be granted with an exercise price lower than set forth in the preceding sentence if such Option is granted pursuant to an assumption or substitution for another option in a manner satisfying the provisions of Section 424(a) of the Code.

11. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) If any change is made in the stock subject to the

Plan, or subject to any Stock Award granted under the Plan (through merger, consolidation, reorganization, recapitalization, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or otherwise), the Plan and outstanding Stock Awards will be appropriately adjusted in the class(es) and maximum number of shares subject to the Plan or an Option under paragraph 4(c) and the class(es) and number of shares and price per share of stock subject to outstanding Stock Awards.

(b) In the event of: (1) a dissolution or liquidation of the Company; (2) a merger or consolidation in which the Company is not the surviving corporation; or (3) a reverse merger in which the Company is the surviving corporation but the shares of the Company's 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 to the extent permitted by applicable law: (i) any surviving corporation will assume any Stock Awards outstanding under the Plan or will substitute similar Stock Awards for those outstanding under the Plan, or (ii) such Stock Awards will continue in full force and effect. In the event any surviving corporation refuses to assume or continue such Stock Awards, or to substitute similar Stock Awards for those outstanding under the Plan, then, with respect to Stock Awards held by persons then performing services as employees or as consultants or directors for the Company, as the case may be, the time during which such Stock Awards become vested or may be exercised will be accelerated and the Stock Awards terminated if not exercised prior to such event.

12. AMENDMENT OF THE PLAN.

(a) The Board at any time, and from time to time, may amend the Plan. However, except as provided in paragraph 11 relating to adjustments upon changes in stock, no amendment will be effective unless approved by the stockholders of the Company within 12 months before or after the adoption of the amendment, where such amendment requires stockholder approval in order for the Plan to satisfy the requirements of Section 422 of the Code, Rule 16(b)(3) promulgated under the Securities Exchange Act of 1934, as amended or any Nasdaq or securities exchange requirements.

(b) It is expressly contemplated that the Board may amend the Plan in any respect the Board deems necessary or advisable to provide optionees with the maximum benefits provided or to be provided under the provisions of the Code and the regulations promulgated thereunder relating to employee Incentive Stock Options and/or to bring the Plan and/or Incentive Stock Options granted under it into compliance therewith.

(c) Rights and obligations under any Stock Award granted before amendment of the Plan will not be altered or impaired by any amendment of the Plan unless (i) the Company requests the consent of the person to whom the Stock Award was granted and (ii) such person consents in writing.

13. TERMINATION OR SUSPENSION OF THE PLAN.

(a) The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan will terminate on January 31, 2008. No Stock Awards may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) Rights and obligations under any Stock Award granted while the Plan is in effect will not be altered or impaired by suspension or termination of the Plan, except with the consent of the person to whom the Stock Award was granted.

14. EFFECTIVE DATE OF PLAN.

The Plan is effective April 19, 1991.

EXHIBIT 10.19

CONFIDENTIAL TREATMENT REQUESTED UNDER 17 C.F.R. SECTIONS 200.80(b)(4), 200.83 AND 240.24b-2. * INDICATES OMITTED MATERIAL THAT IS THE SUBJECT OF A CONFIDENTIAL TREATMENT REQUEST THAT IS FILED SEPARATELY WITH THE COMMISSION.

==========

ISIS PHARMACEUTICALS, INC.

$50,000,000
14% Senior Subordinated Discount Notes due November 1, 2007
And
Warrants for Common Stock

PURCHASE AGREEMENT

Dated as of October 24, 1997

==========

TABLE OF CONTENTS

PURCHASE AGREEMENT

PURCHASE AGREEMENT, dated as of October 24,1997 (this "Agreement"), between ISIS PHARMACEUTICALS, INC., a Delaware corporation (including any corporation succeeding thereto by merger, consolidation or acquisition of all or substantially all of its assets, the "Company"), and the Purchaser listed on Schedule I hereto (the "Purchaser").

The Company and the Purchaser agree as follows:

ARTICLE I

AUTHORIZATION AND ISSUANCE OF SECURITIES

1.1 AUTHORIZATION OF ISSUE. The Company has duly authorized the issuance of its 14% Senior Subordinated Discount Notes due November 1, 2007, in the aggregate principal amount, at maturity, of $50,000,000 (including all debt securities issued in exchange or replacement therefor, the "Notes"). Each Note shall be substantially in the form of Exhibit A hereto. In order to induce the Purchaser to purchase the Notes and in connection therewith, the Company has duly authorized the issuance of its warrants (the "Warrants") evidencing the right to purchase, in the aggregate, 500,000 shares of Common Stock, $.001 par value per share, of the Company at the Basic Purchase Price (as defined in the Warrants) of $25.00 per share; such number of shares and such Basic Purchase Price being subject to adjustment as provided in the Warrants. Each Warrant shall be substantially in the form of Exhibit B hereto. The Notes and the Warrants hereinafter referred to are herein collectively called the "Securities."

1.2 ISSUANCE OF SECURITIES. (a) Purchase of Notes: Delivery of Warrants. Subject to the terms hereof, (i) the Company agrees to sell, and the Purchaser agrees to purchase, on the Closing Date hereinafter referred to, Notes in the aggregate principal amount, at maturity, of $50,000,000 at a price equal to $25,060,075.13, payable in immediately available funds and (ii) the Company agrees to deliver to the Purchaser, and the Purchaser agrees to accept, on the Closing Date hereinafter referred to, the Warrants evidencing the right to purchase, in the aggregate, 500,000 shares of Common Stock, $.001 par value per share, at the Basic Purchase Price of $25.00 per share, such number of shares and such Basic Purchase Price being subject to adjustment as provided in the Warrants.

(b) Closing Date: Delivery of Notes and Warrants. The date for the purchase and sale of Notes hereunder (the "Closing Date") shall be October 24, 1997, or such other date as may be agreed to by the parties hereto. Purchase and sale of the Notes hereunder shall take place at 1:00 P.M., Eastern Time, on the Closing Date, at the offices

of the Purchaser, (*) or such other place as the parties hereto may designate. On the Closing Date, the Company will deliver to the Purchaser against payment of the purchase price therefor, ten Notes in the aggregate principal amount, at maturity, of $50,000,000, dated the Closing Date and registered in the Purchaser's name or in the name of its nominee, and in connection with the

delivery of the Notes to the Purchaser on the Closing Date, and simultaneously with such delivery, the Company will deliver to the Purchaser ten Warrants, registered in the Purchaser's name or in the name of its nominee, and evidencing the right to purchase an aggregate of 500,000 shares of Common Stock, $.001 par value per share, at the Basic Purchase Price of $25.00 per share, such number of shares and such Basic Purchase Price being subject to adjustment as provided in such Warrant.

1.3 SECURITIES LAWS. (a) The Company's Representation and Agreements. The Company represents and warrants to the Purchaser that the Company has not, directly or through any agent, offered any of the Securities or any similar security for sale to, or solicited any offers to buy any thereof from, or otherwise approached or negotiated in respect thereof with, any Person other than the Purchaser who was offered the Securities in a private sale for investment, and the Company agrees that neither the Company nor any agent acting on the Company's behalf has done or caused to be done or will do or cause to be done or omit to do or cause to be done anything which would result in bringing the issuance or sale of the Notes and the Warrants within the registration requirements of Section 5 of the Securities Act.

(b) The Purchaser's Representations and Agreements. The Purchaser represents and warrants, and in entering into this Agreement the Company understands and acknowledges, that it is acquiring the Securities for its own account for investment purposes and not with a view to, or for sale in connection with, any distribution (as such term is used under Section 2(11) of the Securities Act) thereof. Without limiting the foregoing, the Purchaser acknowledges and agrees that the Securities have not and will not be registered under the Securities Act or any applicable state securities laws and it agrees that it will reoffer or resell the Securities or the Warrant Shares purchased by it under this Agreement (i) only (A) to the Company, (B) pursuant to any transaction under and meeting the requirements of Rule 144A, as amended from time to time, promulgated under the Securities Act, (C) pursuant to an exemption from registration under the Securities Act in accordance with Rule 144, as amended from time to time, promulgated under the Securities Act, or (D) in accordance with any other available exemption from the requirements of Section 5 of the Securities Act and (ii) in accordance with any applicable federal and state securities laws. The Purchaser further agrees to hold the Company harmless from any claim, demand or liability for broker's or finder's placement fees or commissions payable by the Purchaser alleged to have been incurred by Purchaser in connection with this transaction.

ARTICLE II

THE COMPANY'S REPRESENTATIONS AND WARRANTIES

2.1 FINANCIAL INFORMATION. (a) Statements. The Company has heretofore filed all reports, statements and schedules with the Commission required to be filed pursuant to the Exchange Act since January 1, 1992 (the "SEC Reports") and has made available to the Purchaser copies of all SEC Reports. The SEC Reports did not (as of their respective filing dates) contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements made therein, in light of the circumstances under which they were made, not misleading. The audited and unaudited consolidated financial statements of the Company included in the SEC Reports have been prepared in accordance with GAAP applied on a consistent basis and fairly present the financial position of the Company as of the dates thereof and the results of operations and consolidated cash flows for the periods then ended, subject, in the case of the unaudited financial statements, to normal year-end audit adjustments which were not materially adverse to the Company. The Company has no material liabilities, fixed or contingent, other than (i) liabilities fully reflected in said financial statements and (ii) liabilities incurred since December 31, 1996 in the ordinary course of business which in the aggregate have no material adverse effect on the properties, operations or condition, financial or otherwise, of the Company or on the conduct of its businesses.

(b) Debt. The Company has furnished to the Purchaser true, correct and complete copies of each instrument which evidences, or will evidence on the Closing Date, any Debt in excess of $5 million of the Company and each

instrument under which any Debt in excess of $5 million of the Company is or will be issued or by which it is or may be secured.

(c) No Material Adverse Change. Other than changes reflected in the SEC Reports, there has been no material adverse change in the business, prospects, properties, operations or condition, financial or otherwise, of the Company since December 31, 1996, whether or not covered by insurance and whether or not arising from transactions in the ordinary course of business.

2.2 ORGANIZATION, STANDING AND QUALIFICATION OF THE COMPANY. The Company is a corporation duly organized and validly existing and in good standing under the laws of the State of Delaware. The Company has all requisite power to own its properties and to carry on its business as now being conducted and as proposed to be conducted. The Company is qualified to do business as a foreign corporation and is in good standing in each jurisdiction in which failure to so qualify

would materially and adversely affect the business, prospects, properties, operations or condition, financial or otherwise, of the Company.

2.3 CAPITALIZATION. The authorized Capital Stock of the Company consists solely of (i) 50,000,000 shares of Common Stock, par value $.001 per share, of which 26,632,766 shares of Common Stock are outstanding as of October 17, 1997, all of which have been duly authorized and validly issued by the Company and are fully paid, nonassessable and free of preemptive rights and (ii) 15,000,000 shares of Preferred Stock, par value $.001 per share, none of which has been issued. There are no shares of Common Stock held on the date hereof in the treasury of the Company. The issuance and sale of all outstanding shares have been in full compliance with all applicable federal and state securities laws. Except (i) as contemplated in this Agreement and (ii) as otherwise disclosed in the SEC Reports, there are no subscriptions, options, warrants or calls relating to the issuance by the Company of any shares of its Capital Stock, including any right of conversion or exchange under any outstanding security or other instrument. Except as disclosed in SEC Reports, the Company is not subject to any obligation (contingent or otherwise) to repurchase or otherwise acquire or retire any shares of its Capital Stock or any security convertible into or exchangeable for any of its Capital Stock. Except for (i) the Voting Agreement, dated November 9, 1990, between the Company, Stanley T. Crooke and Novartis Pharma AG (formerly known as Ciba-Geigy Limited) ("Novartis") and (ii) Section 8. 1 (d) of the Stock Purchase Agreement dated July 18, 1995, between the Company and Boehringer Ingelheim International GmbH ("Boehringer"), each of which relates solely to the election of one director by Novartis or Boehringer, as the case may be, to the Board of Directors, there are no voting trusts or other agreements or understandings with respect to the voting of the Capital Stock of the Company to which the Company is a party. The Common Stock is vested with all the voting rights in the Company.

2.4 AUTHORIZATION. The Company has full power and authority to execute and deliver this Agreement and to issue, sell and deliver the Securities, to perform its obligations hereunder and thereunder and to engage in the transactions contemplated hereby and thereby. This Agreement has been duly authorized, executed and delivered and constitutes, and the Securities will, upon their issuance, execution and delivery, constitute, the legal, valid and binding obligations of the Company.

2.5 FRANCHISES, LICENSES, AND OTHER RIGHTS. The Company has all franchises, permits, licenses and other authority as are necessary to enable it to conduct the business of the Company, except for such franchises, permits, licenses or authorities which the failure to have do not, individually or in the aggregate, materially and adversely affect the business, prospects, properties, operations or condition, financial or otherwise, of the Company, and the Company is not in default under any of such franchises, permits, licenses or other authority. The Company

possesses all patents, patent rights, trademarks, trademark rights, trade names, trade names rights and copyrights necessary to conduct the business of the Company, without conflict with any valid rights of others, except for such conflicts which would not, individually or in the aggregate, materially and adversely affect the business, prospects, properties, operations or condition, financial or otherwise, of the Company.

2.6 LITIGATION. There is no action, suit or proceeding pending against or, to the best of the Company's knowledge, threatened against the Company before or by any court, governmental authority or arbitrator, which (i) questions, either individually or collectively, the validity of this Agreement, the Securities or the consummation of the transactions herein and therein contemplated, (ii) would result, either individually or collectively, in any material adverse change in the business, prospects, properties, operations or condition, financial or otherwise, of the Company or (iii) would impair, individually or collectively, the ability of the Company to perform its obligations under this Agreement or the Securities.

2.7 INTELLECTUAL PROPERTY. Except as disclosed in the SEC Reports, the Company owns or possesses the rights to use the Intellectual Property, and the Company is not aware of any claim to the contrary or any challenge by any person to the rights of the Company with respect to the Intellectual Property which claim or challenge is material to the business, prospects, properties, operations or condition, financial or otherwise, of the Company.

2.8 TITLE AND LIENS. Except as otherwise disclosed in the SEC Reports, the Company has good and marketable fee simple title to all the real property owned by it, and a good and marketable ownership interest in all the other assets, reflected in the financial statements included in the most recent SEC Report or subsequently acquired by the Company other than that subsequently sold or otherwise disposed of in the ordinary course of business, free and clear of all Liens, except as otherwise disclosed in the SEC Reports.

2.9 LEASES. The Company enjoys adequate possession under all of the leases for the use of personal property and real property under which the Company is a lessee or is operating. All of such leases are valid and subsisting, free and clear of all Liens, except for Liens permitted by Section 7.2, and none of them is in default, except for such defaults which would not, individually or in the aggregate, materially and adversely affect the business, prospects, properties, operations or condition, financial or otherwise, of the Company.

2.10 BURDENSOME AND CONFLICTING AGREEMENTS AND VIOLATIONS OF CHARTER PROVISIONS. The Company is not subject to any charter or other corporate restriction or, to its knowledge after due inquiry, bound by any

agreement or instrument which materially and adversely affects the business, prospects, properties, operations or condition, financial or otherwise, of the Company, other than, with respect to any such agreement or instrument, as disclosed in the SEC Reports. The Company is not (i) in violation of its charter or by-laws or (ii) in default under or in violation of any agreement, or instrument by which it is bound, or of any statute, law, rule or regulation, or of any judgment, decree, writ, injunction, order or award of any arbitrator, court or governmental authority applicable to it any of which would result, individually or collectively, in any material adverse change in the business, prospects, properties, operations or condition, financial or otherwise, of the Company. Neither the authorization, execution and delivery of this Agreement, the Securities, the consummation of the transactions herein and therein contemplated, nor the fulfillment of or compliance with the terms hereof and thereof, will conflict with or result in a breach of any of the terms of the charter or by-laws of the Company or will conflict with or result in a material breach of any other corporate restriction or any statute, law, rule or regulation, or of any judgment, decree, writ, injunction, order or award of any arbitrator, court or governmental authority, or of any agreement or instrument, which is applicable to the Company or by which the Company is bound, or constitute a material default thereunder, or result in the imposition of any material Lien upon any of the properties or assets of the Company.

2.11 CONSENTS AND APPROVALS. The Company has obtained or made all necessary (i) governmental consents, approvals and authorizations, and registrations and filings with governmental authorities other than any notices of sale required to be filed with the Commission under Regulation D pursuant to the Securities Act or any such filings as may be required after the Closing under applicable state securities laws, all of which will be timely filed within the applicable periods therefore; and (ii) consents, approvals, waivers and notifications of stockholders, creditors, lessors and other non-governmental persons, in each case, in connection with the execution and delivery of this Agreement and the Securities and the consummation of the transactions herein and therein contemplated.

2.12 COMPLIANCE WITH ERISA. The Company does not maintain, or contribute to, and it is not otherwise obligated to contribute to, any Plan.

2.13 COMPLIANCE WITH LAWS. Except as disclosed in the SEC Reports, the Company is in compliance with all applicable statutes, law, rules, regulations, decisions and orders of all governmental authorities or any court or arbitral tribunal, including, without limitation, those relating to the use, operation, handling, transportation, disposal or release of hazardous or toxic substances or wastes or relating to the protection or restoration of the environment or human exposure to hazardous or toxic substances or wastes, except where such failure to comply would not, individually or in the aggregate, have a material adverse effect on the business, prospects, properties,

operations or condition, financial or otherwise, of the Company, and the Company is not aware of any pending investigation which would reasonably be expected to lead to such a claim.

2.14 RESERVATION OF SHARES. The shares of Common Stock deliverable upon exercise of the Warrants have been duly authorized and reserved for issuance upon such exercise, free from preemptive rights in favor of the holders of shares of Capital Stock or other securities of the Company.

2.15 DISCLOSURE. This Agreement, the Securities and all other documents, certificates, instruments, reports and statements furnished to the Purchaser by or on behalf of the Company in connection with the transactions contemplated hereby and thereby do not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements contained herein and therein, in light of the circumstances under which they were made, not misleading. Other than facts relating to general economic conditions, there is no fact known to the executive officers of the Company which materially and adversely affects, or which is reasonably likely to materially and adversely affect during the twelve month period commencing on the date hereof, the business, prospects, properties, operations or condition, financial or otherwise, of the Company, which has not been set forth in this Agreement or in the SEC Reports.

2.16 BROKER'S OR FINDER'S COMMISSIONS. No broker's or finder's placement fee or commission will be payable by the Company with respect to the issue of the Securities or any of the transactions contemplated hereby. The Company will hold the Purchaser harmless from any claim, demand or liability for broker's or finder's placement fees or commissions payable by the Company alleged to have been incurred by the Company in connection with this transaction.

ARTICLE III

CLOSING CONDITIONS

The Purchaser's obligation to purchase and pay for the Notes and the Warrants on the Closing Date is subject to the complete satisfaction of the Purchaser, on or before the Closing Date, of the conditions set forth in this Article.

3.1 OPINION OF PURCHASER'S SPECIAL COUNSEL. The Purchaser shall have received from Fried, Frank, Harris, Shriver & Jacobson, special counsel for the Purchaser, an opinion, dated the Closing Date, substantially in the form set forth in Exhibit C hereto.

3.2 OPINION OF COMPANY'S COUNSEL. The Purchaser and its special counsel shall each have received from Cooley Godward LLP, counsel for the Company, an opinion, dated the Closing Date, substantially in the form set forth in Exhibit D hereto.

3.3 REPRESENTATIONS AND WARRANTIES. The Company's representations and warranties contained in Section 1.3(a) and in Article II shall be true on and as of the Closing Date with the same effect as if made on and as of the Closing Date. There shall exist on the Closing Date no Event of Default and no condition or event which, with notice or lapse of time or both, would constitute an Event of Default if the Securities had been outstanding at all times from and after the date hereof, and all agreements and conditions to be performed or satisfied by the Company hereunder on or before the Closing Date shall have been duly performed or satisfied. The Company shall have delivered to the Purchaser a certificate, dated the Closing Date and signed by its Chief Executive Officer or its President or one of its Vice Presidents and by its Secretary or an Assistant Secretary, to each of the foregoing effects.

3.4 CONSENTS AND APPROVALS. The Company shall have delivered to the Purchaser a certificate, dated the Closing Date and signed by its Chief Executive Officer or its President or one of its Vice Presidents, listing any consents, waivers, approvals, authorizations, registrations, filings and notifications of the character referred to in Section 2.11 which are necessary, to which shall be attached evidence, satisfactory to the Purchaser, that the same that are required to be obtained or made prior to the Closing Date have been obtained or made and are in full force and effect, or stating that none is necessary.

3.5 PROCEEDINGS AND DOCUMENTS. All corporate and other proceedings and all documents incident to the transactions contemplated by this Agreement shall be reasonably satisfactory in form and substance to the Purchaser, and the Purchaser shall have received copies of all documents and records relating thereto which the Purchaser may reasonably request.

3.6 LEGALITY OF INVESTMENT. The Purchaser's acquisition of the Securities shall be permitted as of the Closing Date under the provisions of all applicable laws or governmental regulations, and such acquisition shall not subject the Purchaser to any penalty or other onerous condition in or pursuant to any such law or regulation; and the Purchaser shall have received such certificates or other evidence as the Purchaser may reasonably request to establish compliance with this condition.

ARTICLE IV
REGISTRATION, EXCHANGE AND TRANSFER OF NOTES

4.1 AUTHORIZED DENOMINATIONS. The Notes are issuable only as fully registered Notes in denominations of at least $5 million.

4.2 THE NOTE REGISTER; PERSONS DEEMED OWNERS. The Company shall maintain, at its office designated for notices in accordance with Section 14.7, a register for the Notes (the "Note Register"), in which the Company shall record the name and address of the Person in whose name each Note has been issued and the name and address of each transferee and prior owner of each Note. The Company may deem and treat the Person in whose name a Note is so registered as the holder and owner thereof for all purposes and shall not be affected by any notice to the contrary; until due presentment of such Note for registration of transfer as provided in this Article IV.

4.3 ISSUANCE OF NEW NOTES UPON EXCHANGE OR TRANSFER. Upon surrender for exchange or registration of transfer of any Note at the office of the Company designated for notices in accordance with Section 14.7, the Company shall execute and deliver, at its expense, one or more new Notes of the same class of any authorized denominations requested by the Holder of the surrendered

Note, each dated the date to which interest has been paid on the Note so surrendered (or, if no interest has been paid, the date of such surrendered Note), but in the same aggregate unpaid principal amount as such surrendered Note, and registered in the name of such Person or Persons as shall be designated in writing by such Holder. Every Note surrendered for registration of transfer shall be duly endorsed, or be accompanied by a written instrument of transfer duly executed, by the Holder of such Note or by its attorney duly authorized in writing. The Company may condition the issuance of any new Note or Notes in connection with a transfer by any Person other than a Purchaser on the payment of a sum sufficient to cover any stamp tax or other governmental charge imposed in respect of such transfer. Any transfer of a Note is subject to the delivery by the Holder to the Company of a completed and signed Bond Power in the form attached to the Note.

4.4 LOST, STOLEN, DAMAGED AND DESTROYED NOTES. At the request of any Holder, the Company will issue, at its expense, in replacement of any Note or Notes lost, stolen, damaged or destroyed, upon surrender of the mutilated portions thereof, if any, a new Note or Notes of the same denominations, of the same unpaid principal amounts and otherwise of the same class and tenor as, the Note or Notes so lost, stolen, damaged or destroyed. The Company may condition the replacement of a Note reported by a Holder as lost, stolen, damaged or destroyed upon the receipt from such Holder of an indemnity or security reasonably satisfactory to the Company, provided that

if such Holder shall be the Purchaser or its nominee or an institutional investor having assets in excess of $100 million (as disclosed in its last financial statement) or its nominee, the Purchaser's or such institutional investor's agreement of indemnity shall be sufficient for purposes of this Section 4.4.

ARTICLE V.

PAYMENT OF NOTES

5.1 REGULAR METHOD OF PAYMENT. Except as provided in Section 5.2, the principal of, and the premium, if any, and interest on, each Note shall be payable at the office of the Company maintained pursuant to Section 14.7, in lawful money of the United States of America, against presentment of such Note for notation of payment or, in the case of a payment in full of such Note, against surrender thereof.

5.2 HOME OFFICE PAYMENT. So long as the Purchaser or its nominee shall be a Holder, the Company will pay all sums becoming due on each Note held by the Purchaser or such nominee at the address of such Purchaser specified for such purpose in Schedule I hereto, by wire transfer of immediately available funds, or at such other address or by such other method as the Purchaser shall have designated by notice to the Company, without presentment and without notations being made thereon, except that any such Note so paid or prepaid in full shall be surrendered to the Company for cancellation upon written request by the Company therefor. Before selling or otherwise transferring any such Note, the Purchaser will make a notation thereon of the aggregate amount of all payments of principal theretofore made, and of the date to which interest has been paid. If the transferee of any Note is an institutional investor having assets in excess of $100 million (as disclosed in its last financial statement) or its nominee and is the Holder of at least $5 million principal amount of Notes, and shall request the Company to make all payments on account of such Note either by check or by wire transfer of immediately available funds, the Company shall make such payments as specified in such request at an address specified in such request, provided that said institutional investor undertakes in said request the same obligations in respect of such Note as those undertaken by such Purchaser in the immediately preceding sentence.

5.3 LIMITATION ON INTEREST. No provision of this Agreement or of any Note shall require the payment or permit the collection of interest in excess of the maximum which is permitted by law. If any such excess interest is provided for herein or in any Note, or shall be adjudicated to be so provided for, then the Company shall not be obligated to pay such interest in excess of the maximum permitted by law, and the right to demand payment of any such excess interest is hereby waived, any other provisions in this Agreement or in any Note

to the contrary notwithstanding.

5.4 PAYMENT OF PRINCIPAL AND INTEREST. The Company will pay the principal of the Notes on November 1, 2007.

The Company will pay interest on the principal amount of the Notes on each Interest Payment Date, as set forth below, at the rate of 14% per annum.

Interest will be paid quarterly in arrears on each Interest Payment Date, commencing on February 1, 2003; provided that no interest shall accrue on the principal amount of the Notes prior to November 1, 2002.

Interest on the Notes will accrue from the most recent date to which interest has been paid or, if no interest has been paid, from November 1, 2002; provided that, if there is no existing default in the payment of interest and if a Note is authenticated between a Regular Record Date and the next succeeding Interest Payment Date, interest shall accrue from such Interest Payment Date. Interest will be computed on the basis of a 360-day year of twelve 30-day months.

The Company shall pay interest on overdue principal and premium, if any, and interest on overdue installments of interest, to the extent lawful, at the rate set forth in the Notes.

5.5 METHOD OF PAYMENT. The Company will pay interest (except defaulted interest) on the principal amount of the Notes as provided above on each Interest Payment Date to the persons who are Holders (as reflected in the Note Register at the close of business on the January 15, April 15, July 15 and October 15, immediately preceding the Interest Payment Date), in each case, even if the Notes are canceled on registration of transfer, registration of exchange, redemption or repurchase after such record date; provided that, with respect to the payment of principal, the Company will make payment to the Holder that surrenders the Notes to the Company on or after November 1, 2007.

The Company will pay principal, premium, if any, and as provided above, interest in money of the United States that at the time of payment is legal tender for payment of public and private debts. If a payment date is a date other than a Business Day at a place of payment, payment may be made at that place on the next succeeding day that is a Business Day and no interest shall accrue for the intervening period.

ARTICLE VI

AFFIRMATIVE COVENANTS

The Company covenants and agrees that, from the date hereof and as long as any of the Securities shall remain outstanding, (and thereafter to the extent provided in Section 6.8):

6.1 USE OF PROCEEDS. The Company represents, warrants, covenants and agrees that:

(a) the proceeds of the sale of the Securities will be used by the Company, in accordance with applicable law, for the purpose of supporting its research and development programs, and

(b) the Company does not own, directly or indirectly, any "margin security", as defined in Regulation G issued by the Board of Governors of the Federal Reserve System (12 CFR Part 207); and the Company will not use any proceeds from the sale of the Securities to purchase or carry any "security", as defined in Section 3(a)(10) of the Exchange Act, or for any other purpose which would result in any transaction contemplated by this Agreement constituting a "purpose credit" within the meaning of said Regulation G, or

which would involve a violation of Section 7 of the Exchange Act or Regulation T, U or X of said Board of Governors (12 CFR Parts 220, 221 and 224, respectively).

6.2 PRESERVATION OF FRANCHISES AND EXISTENCE. Except as otherwise permitted by this Agreement, the Company will (i) maintain its corporate existence, rights and franchises in full force and effect, and (ii) cause each operating Subsidiary to maintain its respective corporate existence, rights and franchises in full force and effect, provided that nothing in this Section 6.2 shall prevent (x) any merger of a Subsidiary into the Company or another Subsidiary or (y) the Company or any Subsidiary from discontinuing any material operations in any particular state or jurisdiction or at any particular location or locations within the state or jurisdiction, or prevent the corporate existence, rights and franchises of any Subsidiary from being terminated if, in the opinion of the Board of Directors of the Company, such discontinuance or termination will not adversely affect the Holders, and if such discontinuance or termination is not in violation of any provision of this Agreement.

6.3 INSURANCE. The Company will maintain or cause to be maintained with respect to its properties and business and the properties and businesses of the Subsidiaries, with financially sound and reputable insurers, insurance against such casualties and contingencies of such types and in such amounts as is customary for

corporations engaged in the same or similar business or having similar properties to the ones of the Company.

6.4 PAYMENT OF TAXES AND OTHER CHARGES. The Company will pay, and will cause each of the Subsidiaries to pay, when due, (i) all taxes, assessments and other governmental charges or levies imposed upon it or any of its properties or income, and (ii) all claims or demands of materialmen, mechanics, carriers, warehousemen, landlords and other like Persons which, if unpaid, might result in the creation of a Lien upon any of its properties, subject, in the case of any of the foregoing or any Lien in respect thereof, to Section 7.2.

6.5 COMMISSION AND STOCK EXCHANGE FILINGS. Promptly upon their becoming available, the Company will deliver to each Holder a copy of (i) all regular or periodic reports which the Company or any Subsidiary shall file with the Commission or any national securities exchange or NASDAQ, and (ii) all reports, proxy statements and financial statements delivered or sent by the Company to its stockholders or by any Subsidiary to its stockholders other than the Company.

6.6 COMPLIANCE CERTIFICATES. Within 45 days after the close of each of the first three quarters of each fiscal year of the Company, and within 90 days after the close of each fiscal year of the Company, the Company will deliver to each Holder a certificate, signed by any two of the Chief Executive Officer, the President, the Executive Vice President or the Vice President-Finance of the Company, stating that a review of the activities of the Company and the Subsidiaries during such fiscal quarter or such fiscal year, as the case may be, has been made under such officers' supervision and that no Event of Default or condition or event which, with notice or lapse of time or both, would constitute an Event of Default has occurred, or, if such Event of Default has occurred, specifying the nature and status thereof, and containing computation (in reasonable detail) demonstrating compliance with the provisions of Article VII. Within 15 days after any Holder shall so request, the Company will execute and deliver to such Holder a certificate, signed by any two of the Chief Executive Officer, the President, the Executive Vice President or the Vice President-Finance of the Company, stating that this Agreement and every Security held by or registered in the name of such Holder are unmodified and in full effect (or, if there has been any modification, that this Agreement and every such Security are in full effect as modified, and setting forth such modifications), and either stating that to the knowledge of the signers of such certificate no Event of Default exists hereunder, or specifying each such default of which the signers may have knowledge.

6.7 INSPECTION AND OTHER INFORMATION. Each Holder and such Persons as it may reasonably designate, may visit and inspect any of the properties of the Company or any Subsidiaries, examine their books of account, take extracts

therefrom and discuss the affairs, finances and accounts of the Company or such Subsidiary with its officers and, after providing written notice to the Company, public accountants (and by this provision the Company and each Subsidiary hereby authorize said accountants to discuss with each Holder and such Persons its finances and accounts), at such reasonable times during business hours and with prior notice and as often as such Holder may reasonably desire. The Company will furnish to each Holder such other financial information as it from time to time may reasonably request.

Any information which is furnished pursuant to this Section 6.7 and is designated in writing by the Company as confidential shall be treated as confidential by each Holder and such Persons in accordance with such procedures as such Holder applies generally to information of this kind; provided, however, that each such Holder may disclose any such information (a) as has become generally available to the public (other than by an act of a Holder in violation of this Agreement), (b) as may be required in any report, statement or testimony required to be submitted to any municipal, state or Federal regulatory body having or claiming to have jurisdiction over any such Holder or to the National Association of Insurance Commissioners or similar organization or their successors, (c) as may be required in response to any summons or subpoena or in connection with any litigation, (d) to the extent that any such Holder believes it appropriate in order to comply with any law, order, regulation or ruling applicable to such Holder and (e) to the prospective transferee in connection with any contemplated transfer of any of the Notes by such Holder; and provided, further, that such Holder (i) agrees that it will not trade in any securities of the Company during any time that it is in possession of confidential information that is material and not generally available to the public (except pursuant to clause (e) above) and (ii) in the event that any such Person does not have a duty of confidentiality to such Holder similar in scope to the duty set forth in this Section 6.7, will cause such Person to undertake in writing to be bound by the confidentiality and other provisions of this Section 6.7. Prior to any disclosure by a Holder of any such information designated in writing by the Company as confidential pursuant to clause (b), (c) or (d) above, such Holder will (A) give written notice to the Company and (B) reasonably cooperate with the Company if it seeks a protective order with respect to such disclosure. Prior to any disclosure by a Holder to a prospective transferee pursuant to clause (e) above of any such information designated in writing by the Company as confidential which information has not become generally available to the public, such Holder will (i) give written notice to the Company and (ii) cause such prospective transferee to enter into an undertaking in writing pursuant to which such prospective transferee will agree to be bound by the confidentiality and other provisions of this Section 6.7.

6.8 COST OF THIS FINANCING. Whether or not the transactions contemplated by this Agreement shall be consummated:

(a) Payment of Fees and Expenses. The Company will pay all reasonable costs and expenses of the Purchaser in connection with this Agreement and the consummation of all transactions contemplated hereby, all printing or reproduction expenses relating to transactions contemplated by this Agreement, and the cost of transmitting the Securities to such address as may be requested by the Purchaser, and will pay (on the Closing Date) the reasonable fees, expenses, and disbursements of Fried, Frank, Harris, Shriver & Jacobson, special counsel to the Purchaser for their services in connection therewith, which fees will not exceed $100,000. Without limiting the foregoing, the Company agrees to pay the cost of obtaining a private placement number for the Notes and the Warrants and authorizes the submission of such information as may be required by Standard and Poor's Corporation for the purpose of obtaining such number.

The Company will also pay all reasonable costs and expenses of the Purchaser and each other Holder relating to any future amendment or supplement to this Agreement or any of the Securities (or any proposal for such amendment or supplement) requested by the Company whether or not consummated or any waiver or consent with respect thereto (or any proposal for such waiver or

consent) whether or not consummated, including, but not limited to, out-of-pocket expenses, the reasonable cost of all accounting services required thereby, all printing or reproduction expenses relating to transactions contemplated thereby, and the cost of transmitting the Securities to such address as may be requested by the Purchaser or Holders, and will pay the reasonable fees, expenses, and disbursements of counsel to the Purchaser and Holders for their services in connection therewith.

(b) Reimbursement. The Company will reimburse all costs and expenses of the character referred to in clause (a) of this Section 6.8 which shall have been paid by the Purchaser or any Holder.

(c) Indemnification. The Company will pay and indemnify the Purchaser and each Holder of any of the Securities against, and hold the Purchaser and any other Holder of any of the Securities harmless from, any and all liability, loss, claim and damage and related expenses, including counsel fees and expenses, incurred by or asserted against the Purchaser or any such Holder arising out of, relating to or as a result of (i) the consummation of the transactions contemplated hereby, (ii) the use of any of the proceeds of the sale of the Securities or (iii) any claim, litigation, investigation or proceeding relating to any of the foregoing, whether or not the Purchaser or any such Holder is a party thereto.

The obligations of the Company under this Section 6.8 shall survive the payment or transfer of the Notes or the expiration or transfer of the Warrants.

6.9 COMPLIANCE WITH LAWS. The Company will, and will cause each Subsidiary to, comply with all applicable statutes, rules, regulations and orders of all governmental authorities, with respect to the conduct of its business and the ownership of its properties, including without limitation (i) all applicable statutes, rules, regulations and orders relating to the use, operation, handling, transportation, disposal, or release of hazardous or toxic substances or wastes or relating to the protection or restoration of the environment or human exposure to hazardous or toxic substances or wastes, (ii) the Occupational Safety and Health Act of 1970, as amended, and (iii) ERISA, if failure to so comply, individually or in the aggregate, could have a material adverse effect on the business, properties, operations or condition, financial or otherwise, of the Company.

6. 1 0 FINANCIAL REPORTS AND BOOKS AND RECORDS. The Company will keep proper books of record and account with respect to a dealings or transactions of the business and affairs of the Company, in accordance with GAAP, and will furnish to each Holder:

(a) Interim Statements. Within 45 days after the end of each of the first three fiscal quarters of each fiscal year of the Company, copies of the unaudited financial statements of the Company and its subsidiaries that are customarily provided by the Company for reporting purposes, all in reasonable detail and certified by an executive officer of the Company as presenting fairly the financial position of the Company; provided that so long as the Company is subject to the reporting requirements of the Exchange Act, the Company may satisfy this requirement by delivery of the Form 1O-Q filed by it with the Commission promptly after the filing thereof.

(b) Annual Statements. Within 90 days after the close of each fiscal year of the Company, copies of consolidated financial statements of the Company setting forth in comparative form the figures for the preceding fiscal year, all in reasonable detail and accompanied by a report thereon of a firm of independent public accountants selected by the Company, to the effect that the consolidated financial statements present fairly, in all material respects, the consolidated financial position of the Company as of the end of the fiscal year being reported on in conformity with GAAP and that the examination of such accountants in connection with such financial statements has been conducted in accordance with generally accepted auditing standards and included such tests of the accounting records and such other auditing procedures as said accountants deemed necessary; provided that so long as the Company is subject to the reporting requirements of the Exchange Act, the Company may satisfy this requirement by delivery of the Form 10-K filed by it with the

Commission promptly after the filing thereof.

(c) Financial Reports. The provisions of paragraphs (a) and (b) notwithstanding, promptly after the same are available, copies of all financial statements

and reports as the Company shall send or make available generally to its stockholders, including without limitation, periodic reports containing unaudited interim statements of results to the extent such reports are prepared by the Company.

6.11 ERISA REPORTS. The Company shall notify each Holder in a statement of an authorized officer of the Company setting forth in reasonable detail the circumstances surrounding such event within 30 days after the Company has knowledge of, or is notified of, the occurrence of (i) a reportable event (within the meaning of Section 4043 of ERISA) with respect to any Plan; (ii) the institution of any steps by the Company, any ERISA Affiliate, the PBGC or any other Person to terminate or reorganize any Plan; (iii) the institution of any steps by the Company or any ERISA Affiliate to withdraw from any Plan; (iv) a non-exempt "prohibited transaction" within the meaning of Section 406 of ERISA in connection with any Plan; (v) any material increase in the liability of the Company with respect to any post-retirement welfare liability; (vi) any failure to make a required installment or other payment with respect to a Plan, on or prior to the applicable date, pursuant to Section 412(m) of the Code or (vii) the taking of any action by, or the threatening of the taking of any action by, the Internal Revenue Service, the Department of Labor or the PBGC with respect to any of the foregoing.

6.12 PRIVATE PLACEMENT NUMBERS. Within two Business Days after the Closing Date, the Company shall apply to Standard and Poor's Corporation for assignment of a Private Placement Number for the Notes and the Warrants.

ARTICLE VII

NEGATIVE COVENANTS

The Company covenants and agrees that, so long as any of the Notes shall be outstanding:

7.1 LIMITATION ON DEBT. Each Subsidiary will not, and the Company will cause each Subsidiary not to, create, incur, assume, suffer to exist or otherwise become liable for, any Debt, except for:

(i) Debt of any Subsidiary outstanding on October 24, 1997; and

(ii) Debt incurred by any Subsidiary, to any commercial financial institution, for the acquisition by any Subsidiary of plant, property and equipment, which acquisition is reasonably necessary, in the good faith determination of the Board of Directors, for the business of the Company and the Subsidiaries, and which Debt has a term to maturity equal to or less than five years at the date of incurrence thereof.

7.2 LIMITATIONS ON LIENS. The Company will not, and will not permit any Subsidiary to, create, incur, assume or suffer to exist any Lien of any kind upon any of their Intellectual Property, now owned or hereafter acquired, except for (i) any Lien created to secure all or any part of the purchase price, or to secure Debt incurred to pay all or any part of the purchase price, of property or assets acquired by the Company or any Subsidiary in the ordinary course of business at no more than its Fair Market Value, in the good faith determination of the Board of Directors, (ii) any Lien created in

connection with a license of the Company or any Subsidiary and granted by the Company or any Subsidiary in the ordinary course of business provided that the Board of Directors has determined in good faith that the Company or any such Subsidiary has received Fair Market Value for such license or (iii) any Lien arising by reason of (1) any judgment, decree or order of any court, so long as such Lien is adequately bonded or the execution or other enforcement thereof is effectively stayed, any appropriate legal proceedings which may have been duly initiated for the review of such judgment, decree or order shall not have been finally terminated or the period within which such proceedings may be initiated shall not have expired; (2) taxes, assessments and charges not yet delinquent or which are being contested in good faith by appropriate proceedings, provided, that adequate reserves with respect thereto are maintained on the books of the Company or its Subsidiaries, as the case may be; (3) security for payment of workmen's compensation, unemployment insurance or social security benefits or other insurance; or (4) operation of law in favor of mechanics, materialmen, laborers, carriers, lessors, landlords, employees or suppliers or similar Persons, incurred in the ordinary course of business for sums which are not yet delinquent or are being contested in good faith by negotiations or by appropriate proceedings which suspend the collection thereof.

7.3 LIMITATION ON RESTRICTED PAYMENTS. The Company will not, and will not permit any of its Subsidiaries to, directly or indirectly:

(a) declare or pay any dividend on, or make any distribution in respect of, any shares of Capital Stock (excluding dividends or distributions payable in shares of Capital Stock, but including dividends or distributions payable in Redeemable Stock or in options, warrants or other rights to purchase Redeemable Stock (other than dividends on such Redeemable Stock payable in shares of such Redeemable Stock)), or

(b) purchase, redeem, prepay or acquire or retire for value, any Capital Stock (such payments or any other actions described in clauses (a) and (b) above being collectively referred to as "Restricted Payments").

Notwithstanding the foregoing, (i) any Subsidiary may declare and pay dividends or make distributions to the Company and (ii) the Company may issue, purchase, redeem, prepay, acquire or retire for value any shares of Capital Stock of

any Subsidiary or any shares of Capital Stock of the Company which is intended to track the separate performance of a particular Subsidiary.

7.4 CHANGE OF CONTROL. (a) Upon a Change of Control, each Holder shall have the right (the "Change in Control Right") to require that the Company repurchase any or all of such Holder's Notes at the purchase price in cash equal to (i) 105% of the Accreted Value if such Change of Control occurs during the period commencing on the Closing Date and ending on November 1, 1999; (ii) 104% of the Accreted Value if such Change of Control occurs during the period commencing on November 2, 1999 and ending on November 1, 2001; (iii) 103% of the Accreted Value if such Change of Control occurs during the period commencing on November 2, 2001 and ending on November 1, 2003; (iv) 102% of the Accreted Value if such Change of Control occurs during the period commencing on November 2, 2003 and ending on November 1, 2005; and (iv) 101% of the Accreted Value if such Change of Control occurs during the period commencing on November 2, 2005 and ending on November 1, 2007. The Company shall pay the Holder such repurchase price plus accrued and unpaid interest, if any, to the date of repurchase, in accordance with the procedures set forth in paragraphs (b) through (f) of this Section 7.4.

(b) Within 5 days following becoming aware of any Change of Control, the Company shall mail a notice to each Holder with a copy to the Paying Agent stating:

(1) that a Change of Control has occurred and that such Holder has the right to require the Company to repurchase such Holder's Notes, in whole or in part, in integral multiples of $1,000 of

principal amount, at a purchase price in cash equal to the appropriate percentage of the Accreted Value thereof as set forth in clause (a) above plus accrued and unpaid interest, if any, to the date of repurchase;

(2) the circumstance and relevant facts regarding such Change of Control (including, to the extent available, information with respect to pro forma historical income, cash flow and capitalization after giving effect to such Change of Control);

(3) the date on which the Change in Control Right expires (which shall be no earlier than 30 days nor later than 60 days from the date such notice is mailed) (the "Change in Control Expiration Date") and date for the repurchase of Notes within 10 days after the Change in Control Expiration Date;

(4) the current exercise price of the Warrants; and

(5) the procedures determined by the Company, consistent with this Section 7.4, that a Holder must follow in order to have its Notes repurchased.

This notice shall also contain information concerning the business of the Company which the Company in good faith believes will enable such Holders to make an informed decision.

(c) Not later than two Business Days after the close of business on the Change in Control Expiration Date, the Company shall (i) accept for payment Notes or portions thereof tendered pursuant to the Change in Control Right, (ii) deposit with the Paying Agent (which for purposes of this Section 7.4 shall not be the Company) money sufficient in immediately available funds to pay the purchase price of all the Notes or portions thereof so tendered and (iii) deliver to the Paying Agent the Notes or portions thereof which have been properly tendered to and are accepted by the Company. The Paying Agent shall, on the repurchase date, mail or deliver payment to each tendering holder in the amount of the purchase price with respect to the Notes tendered by such holder and accepted by the Company from the funds provided by the Company for such payment, and the Company shall execute and the Paying Agent shall mail and deliver to such Holder a new Note equal in amount to any unpurchased portion of the Note surrendered.

(d) Holders electing to have a Note repurchased will be required to surrender the Note, with an appropriate form duly completed, to the Company at the address specified in the notice on or prior to the Change in Control Expiration Date. Holders will be entitled to withdraw their election if the Paying Agent or the Company receives on or prior to the Change in Control Expiration Date written notice setting forth the name of the Holder, the principal amount of the Note which was delivered for purchase by the Holder and a statement that such Holder is withdrawing his election to have such Note repurchased.

(e) At the time the Company delivers Notes to the Paying Agent which are to be accepted for purchase, the Company will also deliver an Officers' Certificate stating that such Notes are to be accepted by the Company pursuant to and in accordance with the terms of this Section 7.4.

(f) The Company shall comply, to the extent applicable, with the requirements of Section 14(e) of the Exchange Act and any other securities laws or regulations in connection with the repurchase of Notes pursuant to this Section. To the extent that the provisions of any securities laws or regulations conflict with the provisions of this Section, the Company shall comply with the applicable securities laws and

26
regulations and shall not be deemed to have breached its obligations under this Section by virtue thereof

7.5 ASSET SALE. (a) The Company will not, and will not permit any of its Subsidiaries to, participate in an Asset Sale unless (i) such Asset Sale is for not less than the Fair Market Value of the assets sold (as determined by the Board of Directors whose determination shall be conclusive and evidenced by a Board Resolution), (ii) the Company repays, from the proceeds of such Asset Sale, all Senior Indebtedness to the extent the terms of the governing documents therefor require such repayment or prohibit the purchase of the Notes, and (iii) the Net Available Proceeds of such Asset Sale include an amount of cash or Cash-Equivalents sufficient to satisfy, in full, the Company's obligations under this Section.

(b) In the event of an Asset Sale, the Company shall make an offer to purchase Notes (the "Offer to Purchase") at the purchase price in cash equal to (i) 105% of the Accreted Value if such Asset Sale occurs during the period commencing on the Closing Date and ending on November 1, 1999; (ii) 104% of the Accreted Value if such Asset Sale occurs during the period commencing on November 2, 1999 and ending on November 1, 2001; (iii) 103% of the Accreted Value if such Asset Sale occurs during the period commencing on November 2, 2001 and ending on November 1, 2003; (iv) 102% of the Accreted Value if such Asset Sale occurs during the period commencing on November 2, 2003 and ending on November 1, 2005; and (iv) 101% of the Accreted Value if such Asset Sale occurs during the period commencing on November 2, 2005 and ending on November 1, 2007. The Company shall pay the Holder such repurchase price plus accrued and unpaid interest, if any, to the date of repurchase, in accordance with the procedures set forth in paragraphs (b) through (i) of this Section 7.5.

(c) Within 5 days following any Asset Sale, the Company shall mail a notice to each Holder with a copy to the Paying Agent stating:

(1) that an Asset Sale has occurred and that such Holder has the right to require the Company to repurchase such Holder's Notes in whole or in part in integral multiples of $1,000 of principal amount, at a purchase price in cash equal to the appropriate percentage of the Accreted Value thereof as set forth in clause (b) above plus accrued and unpaid interest, if any, to the date of repurchase;

(2) the circumstance and relevant facts regarding such Asset Sale (including information which respect to pro-forma historical income, cash flow and capitalization after giving effect to such Asset Sale);

27

(3) the Expiration Date (which shall be no earlier than 30 days nor later than 60 days from the date such notice is mailed) (the "Expiration Date") and a date for the repurchase of Notes within 10 days after the Expiration Date;

(4) the current exercise price of the Warrants; and

(5) the procedures determined by the Company, consistent with this Section 7.5, that a Holder must follow in order to have its Notes repurchased.

The notice shall also contain information concerning the business of the Company which the Company in good faith believes will enable each Holder to make an informed decision.

(d) Upon the occurrence of an Asset Sale, the Company shall, within five Business Days thereafter, irrevocably deposit with the Paying Agent (which for the purpose of this Section 7.5 shall not be the Company) money in immediately available funds in an amount sufficient to repay the Notes, if all the then outstanding Notes were tendered pursuant to the Offer to Purchase, to be held for payment in accordance herewith. The proceeds may be invested in any Temporary Cash Investment the maturity date of which shall not be later than the Expiration Date. The Company shall be entitled to any interest or dividends accrued, earned or paid on such Temporary Cash Investments, unless an Event of Default shall have occurred and be continuing (in which case, such amounts shall be held for application in accordance with Article VIII hereof). To the extent that the aggregate amount of funds deposited by the Company with the Paying Agent exceeds the aggregate amount required to repurchase the Notes, or portions thereof, to be repurchased pursuant to the Offer to Purchase, the Paying Agent shall promptly after the Business Day following the repurchase date, return such excess to the Company.

(e) Upon the Expiration Date, the Company shall deliver to the Paying Agent the Notes or portions thereof which have been properly tendered to and are to be accepted by the Company. The Paying Agent shall, on the repurchase date, mail or deliver payment to each tendering holder in the amount of the purchase price with respect to the Notes tendered by such Holder and accepted by the Company from the funds provided by the Company for such payment, and the Company shall execute and the Paying Agent shall mail and deliver to such Holder a new Note equal in amount to any unpurchased portion of the Note surrendered.

(f) Holders electing to have a Note repurchased will be required to surrender the Note, with an appropriate form duly completed, to the Company at the

address specified in the notice on or prior to the Expiration Date. Holders will be entitled to withdraw their election if the Paying Agent or the Company receives on or prior to the Expiration Date, a written notice setting forth the name of the Holder, the principal amount of the Note which was delivered for purchase by the Holder and the statement that such Holder is withdrawing his election to have such Note repurchased.

(g) At the time the Company delivers Note's to the Paying Agent which are to be accepted for purchase, the Company will also deliver an Officers' Certificate stating that such Notes are to be accepted by the Company pursuant to and in accordance with the terms of this Section 7.5. A Note shall be deemed to have been accepted for purchase at the time the Paying Agent, directly or through an agent, mails or delivers payment therefor to the surrendering Holder.

(h) The Company shall comply, to the extent applicable, with the requirements of Section 14(e) of the Exchange Act and any other securities laws or regulations in connection with the repurchase of Notes pursuant to this Section 7.5.

(i) The Company will not, and will not permit any Subsidiary to, create or permit to exist or become effective any restriction that would materially impair the ability of the Company to make an Offer to Purchase or, if such offer is made, to pay for Notes tendered for purchase.

7.6 TRANSACTIONS WITH AFFILIATES. The Company will not, and will not permit any Subsidiary to, enter into any transaction or series of similar transactions (including, without limitation, the purchase, sale, lease or exchange of any property, the rendering of any service or the making of any loan or extension of credit) with, or make any payment or transfer to, any Affiliate, unless:

(a) such transaction (or series of related transactions) is entered into in the ordinary course of business and pursuant to the reasonable requirements of the Company's or such Subsidiary's business; and

(b) such transaction or series of related transactions are upon fair and reasonable terms no less favorable to the Company or such Subsidiary than the Company or such Subsidiary would obtain in a comparable arm's-length transaction from a Person who is not an Affiliate.

7.7 REPURCHASE OF NOTES. Neither the Company nor any Subsidiary thereof, directly or indirectly, shall repurchase or make any offer to repurchase any Note unless the offer has been made to repurchase Notes, pro rata, from all Holders of the Notes at the same time and upon the same terms. In case the Company or any Subsidiary thereof repurchases any Notes, such Notes shall thereafter be cancelled and no Notes shall be issued in substitution therefor.

ARTICLE VIII

EVENTS OF DEFAULT AND REMEDIES

8.1 EVENT OF DEFAULT. Each of the following shall constitute an Event of Default under this Agreement:

(a) The Company defaults in the payment of any interest upon any of the Notes as and when the same shall become due and payable, and continuance of such default for a period of five Business Days; or

(b) The Company defaults in the payment of the principal of, or premium, if any, on any of the Notes as and when the same shall become due and payable either at maturity or in connection with any redemption, by declaration or otherwise; or

(c) Any representation or warranty made by the Company in this Agreement shall prove to have been untrue in any material respect as of the date of this Agreement or the Company fails to duly observe or perform any covenant contained in Article VII; or

(d) The Company fails to duly observe or perform any other of the covenants or agreements on the part of the Company set forth in the Notes, in this Agreement or in any Warrant, and such failure shall have continued for a period of 30 days after the date on which the Company obtains knowledge of such failure irrespective of the source; or

(e) An event of default, as defined in any mortgage, indenture or instrument under which there may be issued, or by which there may be secured or evidenced, any Debt of the Company or a Subsidiary (whether such Debt now exists or shall hereafter be created or incurred) shall occur and shall (i) consist of a default in the payment of such Debt at the maturity thereof or (ii) shall result in such Debt being declared due and payable prior to the date on which it would otherwise become due and payable, and such default in payment is not cured or such acceleration shall not be rescinded or annulled prior to any period of grace provided with respect thereto; provided that it shall not be an Event of Default if the principal amount of Debt which is not paid at maturity or the maturity of which is accelerated is less than $1 million; and provided, further, that if, prior to a declaration of acceleration of the maturity of the Note or the entry of judgment in favor of the Holders in a suit, such default shall be remedied or cured by the Company or waived by the holders of such Debt, then the Event of Default hereunder by reason thereof shall be deemed likewise to have been thereupon remedied, cured or waived without further action upon the part of any of the Holders of the Notes; or

(f) A court having jurisdiction over the Company shall

enter a decree or order for relief in respect of the Company in an involuntary case under any applicable bankruptcy, insolvency or other similar law now or hereafter in effect, or appoint a receiver, liquidator, assignee, custodian, trustee, sequestrator (or similar official) of the Company or of substantially all of its property or winding-up or liquidation of its affairs, and such decree or order shall remain unstayed and in effect for a period of sixty consecutive days; or

(g) The Company shall commence a voluntary case under any applicable bankruptcy, insolvency or other similar law now or hereafter in effect or shall consent to the entry of an order for relief in an involuntary case under any such law, or shall consent to the appointment of or taking possession by a receiver, liquidator, assignee, custodian, trustee, sequestrator (or similar official) of the Company or of substantially all of its property, or shall make any general assignment for the benefit of creditors; or

(h) A final judgment or judgments (after the expiration of all times to appeal therefrom) for the payment of money in excess of an amount, in the aggregate, equal to 25% of the total current assets minus the total current liabilities of the Company (as determined in accordance with GAAP), as such assets and liabilities are reflected in the most recent balance sheet of the Company filed with the Commission, shall be rendered against the Company or any Subsidiary of the Company unless the same shall be (i) fully covered by insurance (subject to a reasonable deductible) and the insurer shall have accepted liability therefor in writing or (ii) vacated, stayed, bonded, paid or discharged within a period of 15 days from the date of such judgment.

If an Event of Default shall be continuing, then and in each and every such case, unless the principal of all of the Notes shall have already become due and payable, the Holders of not less than 25% in aggregate face amount of the Notes then outstanding hereunder, by notice in writing to the Company, may declare the Default Amount (as set forth below), and all accrued and unpaid interest thereon, of all the Notes to be due and payable immediately, and upon any such declaration the same shall become and shall be immediately due and payable, anything in this Agreement or in the Notes contained to the contrary notwithstanding; provided, however, that if an Event of Default under clause (f) or (g) above shall have occurred, the Default Amount of all the Notes, and all accrued and unpaid interest thereon, shall immediately become due and payable, anything in this Agreement or in the Notes contained to the contrary notwithstanding, without any declaration and without declaration, demand, protest or other notice whatsoever, all of which are hereby waived.

Prior to November 1, 2002, the "Default Amount" in respect of any particular Note as of any particular date shall be equal to the Accreted Value of the Note

as of such date. On or after November 1, 2002, the Default Amount in respect of any particular Note as of any particular date shall be equal to 100% of the principal amount payable in respect of the Note at its Stated Maturity.

In case the Holders shall have proceeded to enforce any right under this Agreement and such proceedings shall have been discontinued or abandoned because of such rescission or annulment or for any other reason or shall have been determined adversely to the Holders, then and in every such case the Company and the Holders shall be restored respectively to their several positions and rights hereunder, and all rights, remedies and powers of the Company and the Holders shall continue as though no such proceeding had been taken.

8.2 OTHER REMEDIES. If any Event of Default shall be continuing, any Holder may enforce its rights by suit in equity, by action at law, or by any other appropriate proceedings, whether for the specific performance (to the extent permitted by law) of any covenant or agreement contained in this Agreement or in the Notes or in aid of the exercise of any power granted in this Agreement or in any of the Notes, and may enforce the payment of any Note held by such Holder and any of its other legal or equitable rights.

8.3 CONDUCT NO WAIVER; COLLECTION EXPENSES. No course of dealing

on the part of any Holder, nor any delay or failure on the part of any Holder to exercise any of its rights, shall operate as a waiver of such right or otherwise prejudice such Holder's rights, powers and remedies. If the Company fails to pay, when due, the principal of, the premium, if any, or the interest on any Note, or if the Company fails to comply with any other provision of this Agreement, the Company will pay to the Holders, to the extent permitted by law, on demand, such further amounts as shall be sufficient to cover the cost and expenses, including but not limited to reasonable attorneys' fees, incurred by such Holders in collecting any sums due on the Notes or in otherwise enforcing any of their rights.

8.4 REMEDIES CUMULATIVE. No right or remedy conferred upon or reserved to the Purchaser of any Holder under this Agreement is intended to be exclusive of any other right or remedy, an every right and remedy shall be cumulative and in addition to every other right and remedy given hereunder or now or hereafter existing under applicable law. Every right and remedy given by this Agreement or by applicable law to the Purchaser or any Holder may be exercised from time to time and as often as may be deemed expedient by the Purchaser or such Holder, as the case may be.

8.5 COOPERATION BY THE COMPANY. To the extent that it lawfully may, the Company agrees that it will not at any time insist upon or plead, or in any manner whatever claim or take any benefit or advantage of any applicable present or

future stay, extension or moratorium law, which may affect observance or performance of the provisions of this Agreement or of any Security.

ARTICLE IX

DEFINITIONS.

9.1 PREVIOUS DEFINITIONS. The following terms have been elsewhere defined in this Agreement and have the respective meanings assigned to them in the indicated sections, and such terms, together with the other terms defined in Section 9.2, shall include the singular as well as the plural: "Agreement," "Company" and "Purchaser," defined in the introductory paragraph; "Notes," "Warrants" and "Securities," defined in Section 1.1; "Closing Date," defined in Section 1.2(b); "SEC Reports," defined in Section 2.1; "Note Register," defined in Section 4.2; "Restricted Payments," defined in Section 7.3; "Change in Control Right" and "Change in Control Expiration Date," defined in Section 7.4; "Offer to Purchase" and "Expiration Date," defined in Section 7.5; "Default Amount," defined in Section 8.1; "NASDAQ," defined in Section 9.2; "Senior Representative," "Payment Blockage Period" and "Initial Blockage Period," defined in Section 11.3.

9.2 ADDITIONAL DEFINITIONS. Except as otherwise specified or as the context may otherwise require, the following terms shall have the respective meanings set forth below whenever used in this Agreement:

The term "Accreted Value" shall mean, for any Specified Date, the amount provided below for each $1,000 principal amount at maturity of Notes (which shall be calculated by the Company and communicated in writing to the Purchaser and each Holder when required by the terms of this Agreement):

(a) if the Specified Date occurs on one of the following dates (each a "Quarterly Accrual Date"), the Accreted Value will equal the amount set forth below for such Quarterly Accrual Date:

Quarterly Accrual Date	Accreted Value
February 1, 1998	$ 520.16
May 1, 1998	$ 538.36

August 1, 1998	$ 557.20
November 1, 1998	$ 576.71
February 1, 1999	$ 596.89
May 1, 1999	$ 617.78
August 1, 1999	$ 639.40

Quarterly Accrual Date	Accreted Value
November 1, 1999	$ 661.78
February 1, 2000	$ 684.95
May 1, 2000	$ 708.92
August 1, 2000	$ 733.73
November 1, 2000	$ 759.41
February 1, 2001	$ 785.99
May 1, 2001	$ 813.50
August 1, 2001	$ 841.97
November 1, 2001	$ 871.44
February 1, 2002	$ 901.94
May 1, 2002	$ 933.51
August 1, 2002	$ 966.18
November 1, 2002	$1,000.00

(ii) if the Specified Date occurs before the first Quarterly Accrual Date, the Accreted Value will equal the sum of (a) $501.20 and (b) an amount equal to the product of (1) the Accreted Value for the first Quarterly Accrual Date less $501.20 multiplied by (2) a fraction, the numerator of which is the number of days from the date of issue of the Notes to the Specified Date, using a 360-day year of twelve 30-day months, and the denominator of which is the number of days from the date of issue of the Notes to the first Quarterly Accrual Date, using a 360-day year of twelve 30-day months;

(iii) if the Specified Date occurs between two Quarterly Accrual Dates, the Accreted Value will equal the sum of (a) the Accreted Value for the Quarterly Accrual Date immediately preceding such Specified Date and (b) an amount equal to the product of (1) the Accreted Value for the immediately following Quarterly Accrual Date less the Accreted Value for the immediately preceding Quarterly Accrual Date multiplied by (2) a fraction, the numerator of which is the number of days from the immediately preceding Quarterly Accrual Date to the Specified Date, using a 360-day year of twelve 30-day months, and the denominator of which is 90; or

(iv) if the Specified Date occurs after the last Quarterly Accrual Date, the Accreted Value will be equal to $1,000.

The term "Affiliate" shall mean, any Person, directly or indirectly, controlling, controlled by or under direct or indirect common control with the Company or a Subsidiary. For purposes of this definition, a Person shall be deemed to control another Person if the controlling Person owns 10% or more of any class of voting securities of the controlled Person or possesses, directly or indirectly, the power to direct or cause the direction of the management or policies of the controlled Person, whether

through ownership of stock, by contract or otherwise; and the terms "controlling" and "controlled" have meanings correlative to the foregoing.

The term "Asset Sale" shall mean, if the Company and/or its Subsidiaries sell, lease, convey, transfer or otherwise dispose of (including, without limitation, by saleleaseback, merger or consolidation, and whether by operation of law or otherwise) all or substantially all of the assets of the Company and its Subsidiaries, taken as a whole. An Asset Sale shall not include a sale, lease, conveyance, transfer or other disposition by the Company or any of its Subsidiaries to any wholly-owned Subsidiary of the Company or by any Subsidiaries to the Company.

The term "Bankruptcy Law" shall mean Title 11, United States Bankruptcy Code of 1978, as amended, or any similar United States Federal or state law relating to bankruptcy, insolvency, receivership, winding-up, liquidation, reorganization or relief of debtors or any amendment to, succession to or change in any such law.

The term "Board of Directors" shall mean the board of directors of the Company or any duly authorized committee thereof.

The term "Board Resolution" shall mean a copy of a resolution certified by the Secretary or an Assistant Secretary of the Company to have been duly adopted by the Board of Directors and to be in full force and effect on the date of such certification.

The term "Business Day" shall mean any day other than a Saturday, a Sunday or other day on which banking institutions or trust companies in the State of New York are not required to be open.

The term "Capital Stock" of any Person shall mean any and all shares, interests (including partnership interests), rights to purchase, warrants, options, participations or other equivalents of or interests in (however designated) equity of such Person, including any Preferred Stock, but excluding any debt securities convertible into or exchangeable for such equity.

The terms "Cash Equivalents" shall mean (A) any security, maturing not more than six months after the date of acquisition, issued by the United States of America, or an instrumentality or agency thereof and guaranteed fully as to principal, premium, if any, and interest by the United States of America, (B) any certificate of deposit, time deposit, Eurodollar time deposit or bankers' acceptance, maturing not more than six months after the date of acquisition, issued by any lender who was a commercial banking institution that is a member of the Federal Reserve System and that has combined capital and surplus of not less than $100 million, whose debt has a rating, at the time as of which any investment therein is made, of "P-1" (or higher) according to Moody's Investors Service, Inc. or any successor rating agency, or "A-1" (or higher) according to

Standard & Poor's Corporation or any successor rating agency, (C) commercial paper, maturing not more than three months after the date of acquisition, issued by any lender who was a corporation (other than an Affiliate or Subsidiary of the Company) organized and existing under the laws of the United States of America with a rating, at the time as of which any investment therein is made, of "P-1" (or higher) according to Moody's Investors Service, Inc. or any successor rating agency, or "A-1" (or higher) according to Standard & Poor's Corporation or any successor rating agency, and (D) any security, on the date of acquisition by any Person, that is listed on any national securities exchange or trades of which are reported on the National Association of Securities Dealers Automated Quotation System ("NASDAQ").

The term "Change of Control" shall mean an event or series of events by which (i) any "person" (as such term is used in sections 13(d) and 14(d) of the Exchange Act) is or becomes the "beneficial owner" (as defined in Rules 13d-3 and 13d-5 under the Exchange Act, except that a person shall be deemed to have "beneficial ownership" of all shares that any such person has the right to acquire, whether such right is exercisable immediately or only after the passage of time), directly or indirectly, of more than 50% of the aggregate

voting power of all the Capital Stock of the Company normally entitled to vote in the election of directors; or (ii) individuals who on the date of this Agreement constituted the Board of Directors of the Company (together with any new or replacement directors whose election by such Board or whose nomination for election by the stockholders was approved by a vote of a majority of the directors then still in office who were either directors on the date of this Agreement or whose election or nomination was previously so approved) shall cease for any reason to constitute a majority of the Board of Directors then in office.

The term "Code" shall mean the Internal Revenue Code of 1986, as amended.

The term "Commission" shall mean the Securities and Exchange Commission and any other similar or successor agency of the federal government administering the Securities Act or the Exchange Act.

The term "Common Stock" shall mean, when used with reference to the Capital Stock of the Company, the class of stock which, on the date of this Agreement, is designated as common stock of the Company and stock of any class or classes into which such common stock or any such other class may thereafter be changed or reclassified.

The term "Company" shall mean Isis Pharmaceuticals, Inc., a Delaware corporation and its permitted successors and assigns.

The term "Credit Agreement" shall mean that certain $40 million Collaboration Agreement, dated as of July 18, 1995 between the Company, as borrower, and Boehringer, as lender, as the same may be amended, restated, supplemented or otherwise modified from time to time.

The term "Debt" of any Person shall mean at any date, without duplication, (i) all obligations of such Person for borrowed money, (ii) all obligations of such Person evidenced by bonds, debentures, notes, letters of credit or other similar instruments, (iii) all obligations of such Person to pay the deferred purchase price of property or services, or arising under any conditional sales or title retention agreement with respect to property acquired by such Person, except accounts payable arising in the ordinary course of business, (iv) all obligations of such Person as lessee under capital leases (in the amount reflected on the balance sheet of such Person, prepared in accordance with GAAP), (v) all Debt of others Guaranteed by such Person, (vi) all obligations, contingent or otherwise, in connection with letters of credit, acceptance facilities or similar facilities, and (vii) to the extent not otherwise included, obligations under (x) any interest rate protection agreement, interest rate swap, interest rate cap or other interest rate hedge agreement, to or under which such Person is a party (but only to the extent of any net credit exposure thereunder) or (y) any forward foreign exchange contract, currency swap agreement or other similar agreement or arrangement designed to protect such Person against fluctuations in currency values (but only to the extent of any net credit exposure thereunder).

The term "ERISA" shall mean the Employee Retirement Income Security Act of 1974, as amended.

The term "ERISA Affiliate" shall mean any corporation, trade or business that is under common control with the Company or is a member of a controlled group of corporations or an affiliated service group or a controlled group of trades or businesses, as described in Sections 414(b), 414(c) or 414(m) of the Code or Section 4001(a)(14) of ERISA.

The term "Event of Default" shall mean any event specified in Section 8.1, continued for the period of time, if any, and after the giving of notice, if any, therein designated.

The term "Exchange Act" shall mean the Securities Exchange Act of 1934, as amended.

The term "Exchangeable Stock" shall mean any Capital Stock of a Person which is exchangeable or convertible into another security (other than Capital Stock of such Person which is neither Exchangeable Stock nor Redeemable Stock).

The term "Fair Market Value" shall mean, with respect to any asset or property, the sale value that would be obtained in an arm's length transaction between an informed and willing seller under no compulsion to sell and an informed and willing buyer under no compulsion to buy.

The term "GAAP" shall mean generally accepted accounting principles in the United States in effect from time to time, consistently applied.

The term "GAAP Consolidated Adjusted Net Worth" of any Person shall mean, at any date, all amounts which would, in conformity with GAAP, be included under shareholders' equity on a consolidated balance sheet of such Person as at such date, after deducting therefrom goodwill, including any amounts (however designated on the balance sheet) representing the cost of acquisitions of Subsidiaries in excess of underlying tangible assets.

The term "Guarantee" by any Person shall mean, without duplication, any obligation, contingent or otherwise, of such Person directly or indirectly guaranteeing any Debt or other obligation of any other Person and, without limiting the generality of the foregoing, any obligation, direct or indirect, contingent or otherwise, of such Person (i) to purchase or pay (or advance or supply funds for the purchase of payment of) such Debt or other obligation (whether arising by virtue of partnership arrangements, by agreement to purchase assets, goods, securities or services, to take-or-pay, to maintain financial statement conditions or otherwise) or (ii) entered into for the purpose of assuring in any other manner the obligee of such Debt or other obligation of the payment thereof or to protect such obligee against loss in respect thereof (in whole or in part); provided that the term Guarantee shall not include endorsements for collection or deposit in the ordinary course of business. The term "Guarantee" used as a verb has a corresponding meaning.

The term "Holder, of Notes, or other similar terms, shall mean any Person in whose name at the time a particular Note is registered on the books of the Company kept for that purpose in accordance with the terms hereof.

The term "Imperial Bank Note Agreement" shall mean those certain Promissory Notes Secured by a Deed of Trust for an aggregate amount equal to $9.7 million dated as of March 24, 1997 between the Company, as borrower, and Imperial Bank, as lender, as the same may be amended, restated, supplemented or otherwise modified from time to time.

The term "incur" (including the correlative terms "incurred", "incurring", "incurs", and "incurrence"), when used with respect to any Debt, shall mean create, incur, assume, guarantee or in any manner become liable in respect of (including, without limitation, by operation of law) such Debt.

The term "Intellectual Property" shall mean all patents, patent rights and applications, inventions, trade secrets, know-how, proprietary techniques, including processes and substances, trademarks, service marks, trade names, copyrights and licenses described or referred to in the SEC Reports or

owned or used by the Company and the Subsidiaries or which, to the Company's knowledge after reasonable inquiry, are necessary for the conduct of their business as it is presently conducted, or as proposed to be conducted.

The term "Interest Payment Date" shall mean each quarterly interest payment date on February 1, May 1, August I and November 1, of each year, commencing on February 1, 2003.

The term "Lien" shall mean any mortgage or deed of trust, pledge, hypothecation, assignment, deposit arrangement, lien, charge, claim, security interest, easement or encumbrance, or preference, priority, or other security agreement or preferential arrangement of any kind or nature whatsoever (including any conditional sale or title retention agreement, any financing lease having substantially the same economic effect as any of the foregoing, and the filing of, or agreement to give, any financing statement perfecting a security interest under the Uniform Commercial Code of any jurisdiction, other than a protective filing filed in connection with a true lease or a filing in connection with a financing lease which is not required to be capitalized on a balance sheet in accordance with GAAP on the basis of immateriality) with respect to any property of the Company or the Subsidiaries, real or personal, movable or immovable, now owned or hereinafter acquired.

The term "Net Available Proceeds" from any Asset Sale shall mean cash or Cash Equivalents received therefrom by the Company and/or its Subsidiaries, net of (i) all legal, title and recording tax expenses, commissions and other fees and expenses incurred and all Federal, state, foreign and local taxes required to be accrued as a liability as a consequence of such Asset Sale, (ii) all payments made by the Company or its Subsidiaries to pay or repay Debt of the Company or any Subsidiary to the extent the terms of governing documents therefor require such repayment or prohibit the purchase of the Notes, (iii) all payments made by the Company or its Subsidiaries on any Debt which is secured by such assets in accordance with the terms of any Lien upon or with respect to such assets or which must by the terms of such lien, in order to obtain a necessary consent to such Asset Sale or by applicable law, be repaid out of the proceeds from such Asset Sale, (iv) all distributions and other payments made to minority interest holders in subsidiaries of the Company or joint ventures as a result of such Asset Sale and (v) appropriate amounts to be provided by the Company or any Subsidiary thereof, as the case may be, as a reserve in accordance with GAAP against any liabilities associated with such assets and retained by the Company or any Subsidiary thereof, as the case may be, after such Asset Sale, including, without limitation, liabilities under any indemnification

obligations and severance and other employee termination costs associated with such Asset Sale, in each case as determined by the Board of Directors of the Company or Subsidiary, in its reasonable good faith judgment evidenced by a resolution of such Board of Directors.

The term "Non-payment Default" shall mean any event (other than a Payment Default) the occurrence of which entitles one or more Persons to accelerate the maturity of any Senior Indebtedness.

The term "Officers' Certificate" when used with respect to the Company, shall mean a certificate signed by any two of the Chief Executive Officer, the President, the Executive Vice President or the Vice President-Finance of the Company.

The term "Opinion of Counsel" shall mean a written opinion of counsel, who may be legal counsel for the Company, and who shall be acceptable to the Holders of not less than 51% in aggregate principal amount of the Notes then outstanding.

The term "Paying Agent" shall mean any state or national bank or trust company organized under the laws of the United States or any state thereof or the District of Columbia and having capital, surplus and undivided profits aggregating at least $100 million and which has been appointed by the Company as paying agent under this Agreement.

The term "PBGC" shall mean the Pension Benefit Guaranty Corporation, or any successor thereto.

The term "Payment Default" shall mean any default in the payment of any amount of Senior Indebtedness as and when due whether at maturity, by acceleration, upon a date set for prepayment or otherwise, including principal, premium, if any, interest, commitment fees, letter of credit fees or reimbursement obligations in respect of letters of credit under Senior Indebtedness.

The term "Permitted Junior Securities" shall mean (so long as the effect of any exclusion employing this definition is not to cause or permit the Notes (or any securities proposed to be issued as "Permitted Junior Securities") to be treated in any case or proceeding or similar event described in clause (a), (b) or (c) of Section 11.2 as part of the same class of claims as the Senior Indebtedness or any class of claims pari passu with, or senior to, the Senior Indebtedness, for any payment or distribution) debt or equity securities of the Company (or any successor corporation) that are provided for by a plan of reorganization or readjustment and that are subordinated at least to the same extent that the Notes are subordinated to the payment of all Senior Indebtedness then outstanding; provided that (1) if a new corporation results from such reorganization or readjustment, such corporation assumes any Senior Indebtedness not paid in full in cash or, as

acceptable to the holders of Senior Indebtedness, in any other manner in connection with such reorganization or readjustment and (2) the rights of the holders of such Senior Indebtedness are not, without the consent of such holders, altered by such reorganization or readjustment.

The term "Person" shall mean any natural person, corporation, partnership, trust, association, governmental authority or unit, or any other entity, whether acting in an individual, fiduciary or other capacity.

The term "Plan" shall mean any multiemployer plan or single employer plan, as defined in Section 4001 of ERISA that is subject to Title IV of ERISA.

The term "Preferred Stock," as applied to the Capital Stock of any corporation, shall mean Capital Stock of any class or classes (however designated) which is preferred as to the payment of dividends, or as to the distribution of assets upon any voluntary or involuntary liquidation or dissolution of such corporation, over shares of Capital Stock of any other class of such corporation.

The term "Prospectus" shall mean the prospectus included in any Registration Statement, as amended or supplemented by any prospectus supplement, with respect to the terms of the offering of any portion of the Notes or the Warrant Shares, pursuant to any registration, as the case may be, covered by the Registration Statement and by all other amendments and supplements to the prospectus, including post-effective amendments and all material incorporated by reference in such prospectus.

The term "Redeemable Stock" shall mean any Capital Stock that by its terms (or by the terms of any security into which it is convertible or for which it is exchangeable), upon the happening of any event or otherwise matures or its required to be redeemed, in whole or in part, on or prior to the first anniversary of the Stated Maturity of the Notes or is redeemable at the option of the holder thereof, in whole or in part, at any time on or prior to the first anniversary of the Stated Maturity of the Notes.

The term "Redemption Date", when used with respect to any Note to be redeemed, shall mean the date fixed for such redemption by or pursuant to this Agreement.

The term "Redemption Price", when used with respect to any Note to be redeemed, shall mean the price at which it is to be redeemed pursuant to this Agreement.

The term "Registrable Securities" shall mean any Notes. As to any particular Registrable Securities once issued, such securities shall cease to be Registrable Securities when (i) a registration statement with respect to the sale of such securities shall have become effective under the Securities Act and such securities shall have been

disposed of in accordance with such registration statement, (ii) such securities shall have been distributed to the public pursuant to Rule 144 (or any successor provision) under the Securities Act, (iii) such securities shall have been otherwise transferred, new certificates for them not bearing a legend restricting further transfer shall have been delivered by the Company and subsequent disposition of them shall not require registration or qualification of them under the Securities Act, or (iv) such securities shall have ceased to be outstanding.

The term "Registration Expenses" shall mean any and all expenses incident to performance of or compliance with Article X, including, without limitation, (i) all Commission and stock exchange or National Association of Securities Dealers, Inc. registration, filing fees and listing expenses, (ii) all fees and expenses of complying with securities or blue sky laws (including reasonable fees and disbursements of counsel for any underwriters in connection with blue sky qualifications of any Registrable Securities), (iii) all printing, messenger and delivery expenses, (iv) the fees and disbursements of counsel for the Company and of its independent public accountants, including the expenses of any special audits and/or "cold comfort" letters required by or incident to such performance and compliance, (v) the fees and disbursements of counsel retained in connection with such registration by the holders of a majority (by number of shares) of the Registrable Securities being registered, and (vi) any fees and disbursements of underwriters customarily paid by issuers or sellers of securities, including the fees and expenses of any special experts retained in connection with the requested registration.

The term "Registration Statement" shall mean any registration statement of the Company which covers any of the Notes or the Warrant Shares pursuant to the provisions of this Agreement, including the Prospectus, amendments and supplements to such Registration Statement, including post-effective amendments, and all exhibits and all material incorporated by reference in such Registration Statement.

The term "Regular Record Date" for the interest payable on any Interest Payment Date shall mean the January 15, April 15, July 15 and October 15 (whether or not a Business Day), as the case may be, next preceding such Interest Payment Date.

The term "Securities Act" shall mean the Securities Act of 1933, as amended.

The term "Senior Indebtedness" shall mean the principal of, premium, if any, and interest (including interest accruing after the filing of a petition initiating any proceeding under any state, federal or foreign bankruptcy laws whether or not allowable in such proceeding) on any Debt of the Company (other than as otherwise provided in this definition), whether outstanding on the date of this Agreement or thereafter created, incurred or assumed, and whether at any time owing, actually or contingent, unless, in the

case of any particular Debt, the instrument creating or evidencing the same or pursuant to which the same is outstanding expressly provides that such Debt shall not be senior in right of payment to the Notes. Without limiting the generality of the foregoing, "Senior Indebtedness" shall include the principal of, premium, if any, and interest (including interest accruing after the filing

of a petition initiating any proceeding under any state, federal or foreign bankruptcy laws whether or not allowable in such proceeding) on all monetary obligations of every kind and nature of the Company from time to time owed under the (i) Credit Agreement and (ii) Imperial Bank Note Agreement, including fees, reimbursement obligations in respect of letters of credit (or guarantees thereof) and indemnity and expense reimbursement obligations thereof; provided, however, that any Debt under any refinancing, refunding, or replacement of the Credit Agreement shall not constitute Senior Indebtedness to the extent that the Debt thereunder is by its express terms subordinate to the Notes. Notwithstanding the foregoing, "Senior Indebtedness" shall not include (i) any Debt that expressly provides that it is subordinate or junior in right of payment to the Notes, (ii) any liability for foreign, federal, state, local or other taxes owed or owing by the Company, (iii) any Debt of the Company to a Subsidiary or any other Affiliate of the Company or any of such Affiliate's subsidiaries and (iv) that portion of any Debt which at the time of incurrence is issued in violation of this Agreement.

The term "Specified Date" means any Redemption Date, any payment date for an Offer to Purchase pursuant to Section 7.4 or Section 7.5 or any date on which the Notes are due and payable after an Event of Default.

The term "Stated Maturity" shall mean, with respect to any security, the date specified in such security as the fixed date on which the principal of such security is due and payable, including pursuant to any mandatory redemption provision (but excluding any provision providing for the repurchase of such security at the option of the holder thereof upon the happening of any contingency).

The term "Subordinated Indebtedness" shall mean Debt which is subordinate in right of payment and on liquidation to the Notes.

The term "Subsidiary" shall mean, with respect to any Person, any corporation or entity of which a majority of the Capital Stock or other ownership interests having ordinary voting power to elect a majority of the Board of Directors or other Persons performing similar functions is at the time directly or indirectly owned by such Person and/or by one or more other Subsidiaries. Unless the context otherwise requires, the term "Subsidiary" as used herein, means a Subsidiary of the Company.

The term "Temporary Cash Investment" shall mean (A) any evidence of Debt, maturing not more than one year after the date of acquisition, issued by the United

States of America, or an instrumentality or agency thereof and guaranteed fully as to principal, premium, if any, and interest by the United States of America, (B) any certificate of deposit, maturing not more than one year after the date of acquisition, issued by, or time deposit of, any lender who was a commercial banking institution that is a member of the Federal Reserve System and that has combined capital and surplus and undivided profits of not less than $100 million, whose debt has a rating, at the time as of which any investment therein is made, of "P-1" (or higher) according to Moody's Investors Service, Inc. or any successor rating agency, or "A-1" (or higher) according to Standard & Poor's Corporation or any successor rating agency, (C) commercial paper, maturing not more than one year after the date of acquisition, issued by any lender who was a corporation (other than an Affiliate or Subsidiary of the Company) organized and existed under the laws of the United States of America with a rating, at the time as of which any investment therein is made, of "P-1" (or higher) according to Moody's Investors Service, Inc. or any successor rating agency, or "A-1" (or higher) according to Standard & Poor's Corporation or any successor rating agency, and (D) any money market deposit accounts issued or offered by any lender who was an original signatory to the Credit Agreement or a domestic commercial bank having capital and surplus in excess of $100 million.

The term "Trust Indenture Act" shall mean the Trust Indenture Act of 1939, and any similar or successor federal statute, and the rules and regulations of the Commission thereunder, all as the same may be in effect at

the time.

The term "Warrant Shares" shall have the meaning specified in the Warrants.

9.3 ACCOUNTING PRINCIPLES. The character or amount of any asset, liability, capital account or reserve and of any item of income or expense required to be determined pursuant to this Agreement, and any consolidation or other accounting computation required to be made pursuant to this Agreement, and the construction of any definition in this Agreement containing a financial term, shall be determined or made, as the case may be, in accordance with GAAP, to the extent applicable, unless such principles are inconsistent with the express requirements of this Agreement.

9.4 DIRECTLY OR INDIRECTLY. If any provision in this Agreement refers to any action taken or to be taken by any Person, or which such Person is prohibited from taking, such provision shall be applicable whether such action is taken directly or indirectly by such Person, whether or not expressly specified in such provision.

ARTICLE X

REGISTRATION RIGHTS

10.1 REGISTRATION REQUESTED BY THE HOLDERS. (1) At any time and from time to time after the date hereof, Holders of Registrable Securities shall have the right to request to the Company to effect the registration under the Securities Act of all or part of such Holders' Registrable Securities. Upon receipt of such request, the Company shall promptly give notice of such proposed registration to all Holders and thereupon shall, as expeditiously as possible, use its best efforts to effect the registration under the Securities Act of.

(i) all Registrable Securities which the Company has been requested to register pursuant to clause (1) of this Section 10.1; and

(ii) all other Registrable Securities which Holders have, within 20 days after the Company has given such notice, requested the Company to register;

all to the extent requisite to permit the sale or other disposition by the Holders of the Registrable Securities so to be registered.

(2) If the managing underwriter of the public offering to be effected pursuant to a registration statement filed pursuant to this clause (1) of Section 10.1 shall advise the Company in writing (with a copy to each holder of Registrable Securities requesting registration) that, in its opinion, the number of securities requested to be included in such registration (including securities of the Company which are not Registrable Securities) exceeds the number which can be sold in such offering, the Company will include in such registration to the extent of the number which the Company is so advised can be sold in such offering:

(i) first, Registrable Securities requested to be included in such registration by the Holders pursuant to clauses (i) and (ii) of Section 10.1, pro rata among such Holders on the basis of the number of shares of Registrable Securities requested to be included by each; and

(ii) second, other securities of the Company proposed to be included in such registration, in accordance with the priorities, if any, then existing among the Company and the holders of such other securities.

(3) Notwithstanding the foregoing, in the event that the Company proposes to include newly issued securities in any registration statement and offering pursuant to clause (1) of this Section 10.1 and such securities would be excluded from

45
such offering by operation of the priority provisions set forth above, the Company may elect to cause such registration statement to be filed under Section 10.2; provided, however, that the Company may make such election no more than once. In the event that the Company makes such election, all of the provisions of Section 10.2 shall apply to such registration and such registration shall not be deemed to be a registration pursuant to Section 10.1.

(4) The Holders requesting inclusion in a registration statement under this Section 10.1 may withdraw from any requested registration pursuant to this Section 10.1 by giving written notice to the Company prior to the filing date of such registration statement; provided, however, that for a period of three months after such withdrawal, such Holders may not request any registration pursuant to this Section 10.1.

(5) The Company shall not be required to effect more than a total of two effective registrations under this Section 10.1.

(6) The Company shall not be required to effect a registration pursuant to this Section 10.1 unless the offering includes at least $12.5 million aggregate face amount of Registrable Securities.

10.2 "PIGGYBACK" REGISTRATIONS. If the Company at any time proposes to register any of its securities under the Securities Act (other than pursuant to Section 10.1) on a registration statement on Form S-1, S-2 or S-3 or on any other form upon which may be registered securities similar to the Registrable Securities for sale to the general public, the Company will at each such time give prompt notice to all Holders of its intention to do so setting forth the date on which the Company proposes to file such registration statement, which date shall be no earlier than 30 days from the date of such notice, and advising each such Holder of its right to have its Registrable Securities included therein. Upon the written request of any Holder given to the Company not less than 5 days prior to the proposed filing date of such registration statement set forth in such the Company notice, the Company will use its best efforts to cause each of the Registrable Securities which the Company has been requested to register by such Holder to be registered under the Securities Act. If the securities to be so registered for sale include securities to be sold for the account of the Company and to be distributed by or through a firm of underwriters of recognized standing under underwriting terms appropriate for such transaction, then the Registrable Securities shall also be included in such underwriting, provided that if, in the reasonable written opinion of the managing underwriter or underwriters, the total amount of such securities to be so registered, when added to such Registrable Securities, will exceed the maximum amount of the Company securities which can be marketed (i) at a price reasonably related to their then current market value, or (ii) without otherwise materially and adversely affecting the entire

46
offering, the Company will include in such registration to the extent of the number which the Company is so advised can be sold in such offering securities determined as follows:

(1) if such registration as initially proposed by the Company was solely a primary registration of its securities:

(i) first, the securities proposed by the Company to be sold for its own account,

(ii) second, any Registrable Securities requested to be included in such registration pro rata among the holders of such Registrable Securities and the holders of such other securities of the Company on the basis of the number of Registrable Securities and other securities of the Company requested to be included by each such holder, and

(iii) third, any other securities of the Company proposed to be included in such registration statement in accordance with the provisions, if any, then existing among the holders of such securities, and

(2) if such registration as initially proposed by the Company was in whole or in part requested by holders of securities of the Company, other than holders of Registrable Securities, pursuant to demand registration rights,

(i) first, such securities held by the holders initiating such registration, pro rata among the holders thereof, on the basis agreed upon by such holders and the Company,

(ii) second, Registrable Securities requested to be included in such registration pro rata among the holders of such Registrable Securities and the holders of such other securities on the basis of the number of Registrable Securities and other securities of the Company requested to be included by each such holder, and

(iii) third, any other securities of the Company proposed to be included in such registration statement in accordance with the priorities, if any, then existing among the holders of such securities.

Each Holder for the account of which any Registrable Securities shall be included in such underwriting shall agree not to sell any other Registrable Securities then held by such Holder until 120 days after the effective date of such registration statement, except that such Holder may sell such other Registrable Securities in private transactions within such period to transferees who agree not to sell such securities within the remainder of such

120-day period. Any registration of Registrable Securities pursuant to this Section 10.2 shall have no effect on any registration pursuant to Section 10.1.

10.3 THE COMPANY'S OBLIGATIONS IN REGISTRATION. If and whenever the Company is obligated by the provisions of this Article X to use its best efforts to effect the registration of any Registrable Securities under the Securities Act, as expeditiously as possible the Company will:

(1) prepare and file with the Commission, as expeditiously as possible within 60 days after the initial request from Holders to register such Registrable Securities, a registration statement with respect to such Registrable Securities and use its best efforts to cause such registration statement to become effective within 120 days after such initial request and to remain effective; provided, however, that the Company shall not be required to keep such registration statement effective, or to prepare and file any amendments or supplements thereto, later than 5 P.M., Eastern Time, on the last Business Day of the ninth month following the date on which such registration statement becomes effective under the Securities Act or such longer period during which the Commission requires that such registration statement be kept effective with respect to any of the Registrable Securities so registered;

(2) prepare and file with the Commission such amendments and supplements to such registration statement and the prospectus used in connection therewith as may be necessary to keep such registration statement effective and to comply with provisions of the Securities Act with respect to the disposition of all Registrable Securities covered by such registration statement whenever the Holders for whom such Registrable Securities are registered or are to be registered shall desire to dispose of the same, subject, however, to the proviso contained in the immediately preceding clause (1);

(3) furnish to the Holders for whom such Registrable Securities are registered or are to be registered, such numbers of copies of a printed prospectus, including a preliminary prospectus and any amendments or supplements thereto, in conformity with the requirements of the Securities Act, and such other documents and information as such Holders may reasonably request in order to facilitate the disposition of such Registrable Securities or in order to conduct any investigation of the Company in connection with the registration of such Registrable Securities;

(4) use its best efforts to register or qualify the Registrable Securities covered by such registration statement under such other securities or blue sky laws of such jurisdictions as the Holders for whom such Registrable Securities are registered or are to be registered shall request, and do any and all other acts and things which may be necessary or advisable to enable such Holders to consummate the disposition in such jurisdictions of such Registrable Securities except that the Company

shall not for any purpose be required to (i) qualify generally to do business as a foreign corporation in any jurisdiction wherein it would not but for the requirements of this clause (4) be obligated to be so qualified, (ii) subject itself to taxation in any such jurisdiction or (iii) consent to general service of process in any such jurisdiction unless the Company is already subject to service of process in such jurisdiction;

(5) furnish to the Holders for whom such Registrable Securities are registered or are to be registered at the time of the disposition of such Registrable Securities by such Holders a signed copy of an opinion of counsel for the Company acceptable to such Holders as to such matters as such Holders may request and substantially to the effect that, a registration statement covering such Registrable Securities has been filed with the Commission under the Securities Act and has been made effective by order of the Commission; said registration statement and the prospectus contained therein comply as to form in all material respects with the requirements of the Securities Act and, based upon such investigation and inquiry as said counsel deems necessary or appropriate, nothing has come to said counsel's attention which would cause it to believe that either said registration statement or said prospectus contains an untrue statement of a material fact or omits to state a material fact required to be stated therein or necessary to make the statements therein (in the case of said prospectus, in the light of the circumstances under which they were made) not misleading; said counsel knows of no legal or governmental proceedings required to be described in said prospectus which are not described as required, or of any contract or documents of a character required to be described in said registration statement or said prospectus or to be filed as an exhibit to said registration statement or to be incorporated by reference therein which is not described and filed as required; no stop order has been issued by the Commission suspending the effectiveness of such registration statement and that, to the best of such counsel's knowledge, no proceedings for the issuance of such a stop order are threatened or contemplated; and the applicable provisions of the securities or blue sky laws of each state in which the Company shall be required, pursuant to clause (4) of this Section, to register or qualify such Registrable Securities, have been complied with, assuming the accuracy and completeness of the information furnished to such counsel with respect to each filing relating to such laws; it being understood that said counsel may rely, as to all factual matters and financial data treated therein, on certificates of the Company (copies of which shall be delivered to such Holders), and as to all questions of the laws of each state in which the Company shall be so required to register or qualify such Registrable Securities, on the opinion of counsel from such state reasonably acceptable to such Holders, copies of which shall be delivered to such Holders;

(6) immediately notify each Holder for whom such Registrable Securities are covered by such registration statement, at any time when a prospectus relating thereto is required to be delivered under the Securities Act, of the happening of any event as a result of which the prospectus included in such registration statement, as

then in effect, includes an untrue statement of a material fact or omits to state any material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances under which they were made, and at the request of any such Holder promptly prepare and furnish to such Holder a reasonable number of copies of a supplement to or an amendment of such prospectus as may be necessary so that, as thereafter delivered to the purchasers of such securities, such prospectus shall not include an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances under which they were made;

(7) advise each Holder of Registrable Securities covered by such Registration Statement, promptly after it shall receive notice or obtain knowledge thereof, of the issuance of any stop order by the Commission suspending the effectiveness of such Registration Statement or the initiation or threatening of any proceeding for that purpose; and use its reasonable efforts to comply with all applicable rules and regulations of the Commission, and make

generally available to the Holders of any Registrable Securities covered by such Registration Statement, earnings statements satisfying the provisions of Section 11(a) of the Securities Act, no later than forty-five (45) days after the end of any twelve (12) month period (or ninety (90) days, if such period is a fiscal year) (a) commencing at the end of any fiscal quarter in which Securities are sold to underwriters in an underwritten offering, or (b) if not sold to underwriters in such an offering, beginning with the first day of the month of the Company's first fiscal quarter commencing after the effective date of a Registration Statement;

(8) permit any Holder holding Registrable Securities covered by such Registration Statement or Prospectus to withdraw their Registrable Securities from such Registration Statement or Prospectus if such Holder has informed the Company that it believes that such amendment or supplement does not comply in all material respects with the requirements of the Securities Act or the rules and regulations thereunder, after having been furnished with a copy thereof at least five (5) business days prior to the filing thereof;

(9) enter into such customary agreements (including an underwriting agreement in customary form) and take all such other actions as Holders of a majority in aggregate face amount of the Registrable Securities being sold or the underwriters retained by such Holders, if any, reasonably request in order to expedite or facilitate the disposition of such Registrable Securities, including customary opinions and indemnification;

(10) make available for inspection by any Holder of any Registrable Securities covered by such Registration Statement, any underwriter participating in any disposition pursuant to such Registration Statement, and any attorney, accountant or other

agent retained by any such Holder or underwriter (collectively, the "Inspectors"), all financial and other records, pertinent corporate documents and properties of the Company and its subsidiaries (collectively, the "Records"), if any, as shall be reasonably necessary to enable them to exercise their due diligence responsibility, and cause the Company's and its subsidiaries' directors, officers and employees to supply all information and respond to all inquiries reasonably requested by any such Inspector in connection with such Registration Statement. Holders of Registrable Securities agree that Records and other information which the Company determines in good faith to be confidential, and of which determination the Inspectors and Holders are so notified, shall not be disclosed by the Inspectors or the Holders unless (a) the disclosure of such Records is necessary to avoid or correct a misstatement or omission in the Registration Statement or (b) the release of such Records is required pursuant to a subpoena or court order. Holders of Registrable Securities agree that they will, upon learning that disclosure of the Records is being sought in a court of competent jurisdiction or by a government agency, give prompt notice to the Company and allow the Company to undertake appropriate action to prevent disclosure of the Records deemed confidential;

(11) if requested by the managing underwriters or a Holder of Registrable Securities being sold in connection with an underwritten offering, promptly incorporate in a Prospectus supplement or post-effective amendment such information as the managing underwriters and the Holders of a majority in aggregate face amount of the Registrable Securities being sold agree should be included therein relating to the plan of distribution with respect to such Registrable Securities including, without limitation, information with respect to the securities being sold to such underwriters, the purchase price being paid therefor by such underwriters and with respect to any other terms of the underwritten offering of the Registrable Securities to be sold in such offering; and make all required filings of such Prospectus supplement or post-effective amendment as soon as notified of the matters to be incorporated in such Prospectus supplement or post-effective amendment; and

(12) obtain a CUSIP number for all Registrable Securities (unless already obtained) not later than the Effective Date.

10.4 PAYMENT OF REGISTRATION EXPENSES. The Company shall pay all Registration Expenses in connection with each registration pursuant to this Article X.

10.5 INFORMATION FROM HOLDERS. Notices and requests delivered by Holders to the Company pursuant to this Article X shall contain such information regarding the Registrable Securities to be so registered and the intended method of disposition thereof as shall reasonably be required in connection with the action to be taken.

10.6 INDEMNIFICATION.

(1) Indemnification by the Company. In the event of any registration under the Securities Act of any Registrable Securities pursuant to this Article X, the Company hereby agrees to indemnify and hold harmless each Holder disposing of such Registrable Securities, its respective agents, directors and officers, each other person, if any, who controls (within the meaning of the Securities Act) such Holder and each other person (including underwriters) who participates in the offering of such Registrable Securities, against any losses, claims, damages or liabilities, to the extent that such losses, claims, damages or liabilities (or proceedings in respect thereof) arise out of or are based upon any untrue statement or alleged untrue statement of any material fact contained in any registration statement, on the effective date thereof, under which such Registrable Securities were registered under the Securities Act, in any preliminary prospectus or final prospectus contained therein or in any amendment or supplement to any preliminary prospectus or final prospectus (if used during the period the Company is required to keep such registration statement current in any such case), or arise out of or are based upon the omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, and will reimburse such Holder, such agents, directors and officers and each such controlling person or participating person (including underwriters) for any legal or any other expenses reasonably incurred by such Holder, such agents, directors and officers or such controlling person or participating person (including underwriters) in connection with investigating or defending any such loss, claim, damage, liability or proceeding, provided, that the Company will not be liable in any such case to the extent that any such loss, claim, damage or liability arises out of or is based upon an untrue statement or alleged untrue statement or omission or alleged omission made in such registration statement, said preliminary or final prospectus or said amendment or supplement in reliance upon and in conformity with written information furnished to the Company by an instrument duly executed by such Holder or such controlling or participating person (including underwriters), as the case may be, specifically for use in the preparation of such registration statement; and provided, further, that, with respect to any untrue statement or omission or alleged untrue statement or omission made in any preliminary prospectus, the Company will not be liable to any Holder to the extent that any loss, claim, damage, liability or expense results from the fact that a current copy of the final prospectus was not sent or given to the Person asserting any such loss, claim, damage, liability or expense at or prior to the written confirmation of the sale of the Registrable Securities concerned to such Person if it is determined that it was the responsibility of such Holder to provide such Person with a current copy of the final prospectus and such current copy of the final prospectus was provided to such Holder and would have cured the defect giving rise to such loss, claim, damage, liability or expense. The Company agrees to provide for

contributions relating to such indemnification as shall be reasonably requested by any Holder disposing of any Registrable Securities or by any such underwriter.

(2) Indemnification by Holders. Each such Holder hereby agrees to indemnify and hold harmless the Company, its respective agents, directors and officers, each other person, if any, who controls (within the meaning of the Securities Act) the Company and each other person (including underwriters) who participates in the offering of such Registrable Securities, against all losses, claims, damages and liabilities to which the Company may become subject under the Securities Act or otherwise, insofar as such losses, claims, damages or liabilities arise out of or are based upon any untrue statement of any material fact contained in any such registration statement, on the effective date thereof, under which such Registrable Securities were registered under the Securities Act, in any preliminary prospectus or final prospectus contained

therein or in any amendment or supplement to any preliminary prospectus or final prospectus (if used during the period the Company is required to keep such registration statement current in any such case), or arise out of or are based upon the omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, to the extent that any such loss, claim, damage or liability arises out of or is based upon any such statement or omission made in such registration statement, said preliminary or final prospectus or said amendment or supplement in reliance upon and in conformity with written information furnished to the Company by an instrument duly executed by such Holder and specifically stated to be for use in the preparation of such registration statement.

(3) Notices of Claims, Etc. Each indemnified party, promptly but not later than 30 days after its receipt of notice of the commencement of any action against it in respect of which indemnity may be sought from any indemnifying party or pursuant to this Section 10.6, shall notify such indemnifying party in writing of the commencement thereof. In case any such action shall be brought against any indemnified party and it shall notify such indemnifying party of the commencement thereof, such indemnifying party will be entitled to participate therein and, to the extent that it may wish, to assume the defense thereof, with counsel satisfactory to such indemnified party, and such indemnified party may participate in such defense at such party's expense, and provided, further that the failure of any such indemnified party to give notice as provided herein shall not relieve such indemnifying party of its obligations under this Section 10.6 unless such failure to give notice shall materially adversely affect such indemnifying party in the defense of any such claim or any such litigation. With respect to any claim or litigation being conducted by such indemnifying party, no indemnified party shall, except with the consent of such indemnifying party, consent to entry of any judgment or enter into any settlement of any claim as to which indemnity may be sought. No indemnifying party, in the defense of any such claim or litigation, shall, except with the consent of each indemnified party, consent to entry of any judgment or enter into any settlement which

does not include as an unconditional term thereof the giving by the claimant or plaintiff to such indemnified party of a release from all liability in respect to such claim or litigation.

(4) Contribution. To the extent that the undertaking to indemnity, pay and hold harmless set forth in paragraphs (1) and (2) of this Section 10.6 may be unenforceable because it is violative of any law or public policy, each party that would have been required to provide the indemnity shall contribute the maximum portion which it is permitted to pay and satisfy under applicable law, to the payment and satisfaction of all indemnified liabilities incurred by each party entitled to indemnification under this Section 10.6; provided that in no event shall a Holder be required to contribute an amount greater than the dollar amount of net proceeds received by such Holder with respect to the sale of any Registrable Securities.

10.7 OBLIGATIONS OF THE HOLDERS. Each Holder agrees:

(1) that upon receipt of any notice from the Company of the happening of any event of the kind described in Section 10.3(6), such Holder will forthwith discontinue such Holder's disposition of Registrable Securities pursuant to the registration statement relating to such Registrable Securities until such Holder's receipt of the copies of the supplemented or amended prospectus contemplated by Section 10.3(6) and, if so directed by the Company, will use its best efforts to deliver to the Company (at the Company expense) all copies, other than permanent file copies, then in such Holder's possession of the prospectus relating to such Registrable Securities current at the time of receipt of such notice, and

(2) that it will immediately notify the Company at any time when a prospectus relating to the registration of such Registrable Securities is required to be delivered under the Securities Act, of the happening of any event as a result of which information previously furnished by such Holder to the Company in writing specifically for inclusion in such prospectus contains an untrue statement of a material fact or omits to state any material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances under which they were made. In the event the Company or any such Holder shall give any such notice, the period referred to in

the proviso contained in Section 10.3(1) shall be extended by a number of days equal to the number of days during the period from and including the giving of notice pursuant to Section 10.3(6) to and including the date when each seller of any Registrable Securities covered by such registration statement shall have received the copies of the supplemented or amended prospectus contemplated by Section 10.3(6).

ARTICLE XI

SUBORDINATION OF NOTES

11.1 NOTE SUBORDINATE TO SENIOR INDEBTEDNESS. The Company covenants and agrees, and each Holder of a Note, by his acceptance thereof, likewise covenants and agrees, that, to the extent and in the manner hereinafter set forth in this Article, the Debt represented by the Notes and the payment of the principal of, premium, if any, interest on and any other payment with respect to, each and all of the Notes are hereby expressly made subordinate and subject in right of payment as provided in this Article to the prior payment in full, in cash or, as acceptable to each holder of Senior Indebtedness, in any other manner, of all Senior Indebtedness.

This Article shall constitute a continuing offer to all Persons who, in reliance upon such provisions, become holders of, or continue to hold, Senior Indebtedness; and such provisions are made for the benefit of the holders of Senior Indebtedness; and such holders are made obligees, hereunder and they or each of them may enforce such provisions.

The Notes shall be senior in right of payment and in rights of liquidation to all Subordinated Indebtedness.

11.2 PAYMENT OVER OF PROCEEDS UPON DISSOLUTION, ETC. In the event of (a) any insolvency or bankruptcy case or proceeding, or any receivership, liquidation, reorganization or other similar case or proceeding in connection therewith, relative to the Company or to its creditors, as such, or to its assets, or (b) any liquidation, dissolution or other winding up of the Company, whether voluntary or involuntary and whether or not involving insolvency or bankruptcy, or (c) any assignment for the benefit of creditors or any other marshaling of assets or liabilities of the Company, then and in any such event:

(1) the holders of Senior Indebtedness shall be entitled to receive payment in full in cash or, as acceptable to each holder of Senior Indebtedness, in any other manner, of all amounts due on or in respect of all Senior Indebtedness, before the Holders of the Notes are entitled to receive any payment or distribution of any kind or character (excluding Permitted Junior Securities) on account of principal of, premium, if any, or interest on the Notes (including any payment or other distribution which may be received from the holders of Subordinated Indebtedness as a result of any payment on such Subordinated Indebtedness); and

(2) until all of the Senior Indebtedness is repayed in full as provided in clause (1) above, any payment or distribution of assets of the Company of any

kind or character, whether in cash, property or securities (excluding Permitted Junior Securities), by set-off or otherwise, to which the Holders would be entitled but for the provisions of this Article (including any payment or other distribution which may be received from the holders of Subordinated Indebtedness as a result of any payment on such Subordinated Indebtedness) shall be paid by the liquidating trustee or agent or other Person making such payment or distribution, whether a trustee in bankruptcy, a receiver or liquidating trustee or otherwise, directly to the holders of Senior Indebtedness or their representative or representatives or to the trustee or trustees under any indenture under which any instruments evidencing any of such Senior Indebtedness may have been issued, ratably according to the aggregate amounts remaining unpaid on account of the Senior Indebtedness held or represented by each, to the extent necessary to make payment in full in cash or as acceptable to each holder of Senior Indebtedness, in any other manner, of all Senior Indebtedness

remaining unpaid, after giving effect to any concurrent payment or distribution to the holders of such Senior Indebtedness; and

(3) in the event that, notwithstanding the foregoing provisions of this Section, the Holder of any Note shall have received any payment or distribution of assets of the Company of any kind or character, whether in cash, property or securities, in respect of principal, premium, if any, and interest on the Notes before all Senior Indebtedness is paid in full, then and in such event such payment or distribution (excluding Permitted Junior Securities) (including any payment or other distribution which may be received from the holders of Subordinated Indebtedness as a result of any payment on such Subordinated Indebtedness) shall be paid over or delivered forthwith directly to the holders of Senior Indebtedness or their representative or representatives or to the trustee or trustees under any indenture under which any instruments evidencing any of such Senior Indebtedness have been issued for application to the payment of all Senior Indebtedness remaining unpaid, to the extent necessary to pay all Senior Indebtedness in full in cash or, as acceptable to each holder of Senior Indebtedness, any other manner, after giving effect to any concurrent payment or distribution to or for the holders of Senior Indebtedness.

The consolidation of the Company with, or the merger of the Company with or into, another Person or the liquidation or dissolution of the Company following the conveyance, transfer or lease of its properties and assets substantially as an entirety to another Person upon the terms and conditions set forth in Article XIII shall not be deemed a dissolution, winding up, liquidation, reorganization, assignment for the benefit of creditors or marshaling of assets and liabilities of the Company for the purposes of this Section if the Person formed by such consolidation or the surviving entity of such merger or the Person which acquires by conveyance, transfer or lease such properties and assets substantially as an entirety, as the case may be, shall, as a part of such consolidation, merger, conveyance, transfer or lease, comply with the conditions set forth in Article XIII.

11.3 SUSPENSION OF PAYMENT WHEN SENIOR INDEBTEDNESS IN DEFAULT. (a) Unless Section 11.2 shall be applicable, upon the occurrence and during the continuance of a Payment Default, no cash payment (other than any payments previously made pursuant to Section 11.1 of this Agreement) or distribution of any assets of the Company of any kind or character (excluding Permitted Junior Securities) shall be made by the Company on account of principal of, premium, if any, or interest on, the Notes, or on account of the purchase, redemption or other acquisition of or in respect of the Notes unless and until such Payment Default shall have been cured or waived or shall have ceased to exist or the Senior Indebtedness shall have been discharged or paid in full in cash or in any other manner as acceptable to each holder of such Senior Indebtedness, after which the Company shall (subject to the other provisions of this Article XI) resume making any and all required payments in respect of the Notes, including any missed payments.

(b) Unless Section 11.2 shall be applicable, upon (1) the occurrence and during the continuance of a Non-payment Default and (2) receipt by the Holders and the Company from a representative of the holder of any Senior Indebtedness (collectively a "Senior Representative") or the holder of any Senior Indebtedness of written notice of such Non-payment Default, no payment or distribution of any assets of the Company of any kind or character (excluding Permitted Junior Securities) shall be made by the Company on account of any principal of, premium, if any, or interest on, the Notes, or on account of the purchase, redemption or other acquisition of or in respect of Notes for a period ("Payment Blockage Period") commencing on the date of receipt by the Holders of such notice and continuing until the earliest of (subject to any blockage of payments that may then or thereafter be in effect under subsection (a) of this Section 11.3) (x) 180 days after receipt of such written notice by the Holders (provided that any Senior Indebtedness as to which notice was given shall theretofore have not been accelerated), (y) the date on which such Non-payment Default is cured or waived or ceases to exist or on which the Senior Indebtedness related thereto is discharged or paid in full in cash, or in any other manner as acceptable to the applicable holder of Senior Indebtedness or (z) the date on which such Payment Blockage Period shall have been terminated by written notice to the Company or the Holders from the Senior Representative or holder of Senior Indebtedness initiating such Payment Blockage Period, after which, in the case of clause (x), (y) or (z), the Company shall (subject to the other provisions of this Article including paragraph (a) above) promptly resume

making any and all required payments in respect of the Notes, including any missed payments. Notwithstanding any other provision of this Agreement, in no event shall a Payment Blockage Period under this paragraph (b) extend beyond 180 days from the date of the receipt by the Holders of the notice referred to in clause (2) of this paragraph (b) (the "Initial Blockage Period"). Any number of notices of Nonpayment Defaults may be given during the Initial Blockage Period; provided that during any period of 365 consecutive days only one Payment Blockage Period under this

paragraph (b) may commence and the duration of such period may not exceed 180 days. No Non-payment Default with respect to Senior Indebtedness that existed or was continuing on the date of the commencement of any Payment Blockage Period will be, or can be, made the basis for the commencement of a second Payment Blockage Period, whether or not within a period of 365 consecutive days, unless such Non-payment Default shall have been cured or waived for a period of not less than 90 consecutive days. The Company shall deliver a notice to the Holders promptly after the date on which any Nonpayment Default is cured or waived or ceases to exist or on which the Senior Indebtedness related thereto is discharged or paid in full in cash, or in any other manner as acceptable to each holder of Senior Indebtedness.

(c) In the event that, notwithstanding the foregoing, the Company shall make any payment to the Holder of any Note prohibited by the foregoing provisions of this Section, then and in such event such payment shall be paid over and delivered forthwith to a Senior Representative of the holders of the Senior Indebtedness or as a court of competent jurisdiction shall direct.

11.4 SUBROGATION TO RIGHTS OF HOLDERS OF SENIOR INDEBTEDNESS. After the payment in full, in cash or, as acceptable to each holder of Senior Indebtedness, in any other manner of all Senior Indebtedness, the Holders of the Notes shall be subrogated to the rights of the holders of such Senior Indebtedness to receive payments and distributions of cash, property and securities applicable to the Senior Indebtedness until the principal of, premium, if any, and interest on the Notes shall be paid in full. For purposes of such subrogation, no payments or distributions to the holders of Senior Indebtedness of any cash, property or securities to which the Holders of the Notes would be entitled except for the provisions of this Article, and no payments over pursuant to the provisions of this Article to the holders of Senior Indebtedness by Holders of the Notes, shall, as among the Company, their creditors other than holders of Senior Indebtedness, and the Holders of the Notes, be deemed to be a payment or distribution by the Company to or on account of the Senior Indebtedness.

11.5 PROVISIONS SOLELY TO DEFINE RELATIVE RIGHTS. The provisions of this Article are intended solely for the purpose of defining the relative rights of the Holders of the Notes on the one hand and the holders of Senior Indebtedness on the other hand. Nothing contained in this Article or elsewhere in this Agreement or in the Notes is intended to or shall (a) impair, as among the Company and the Holders of the Notes, the obligation of the Company, which is absolute and unconditional, to pay to the Holders of the Notes the principal of, premium, if any, and interest on the Notes as and when the same shall become due and payable in accordance with their terms; or (b) affect the relative rights of the Holders of the Notes and creditors of the Company other than the rights of the Holders of the Notes in relation to the rights of the holders of Senior Indebtedness; or (c) prevent the Holder of any Note from exercising all remedies

otherwise permitted by applicable law upon default under this Agreement, subject to the rights under this Article of the holders of Senior Indebtedness (1) in any case, proceeding, dissolution, liquidation or other winding up, assignment for the benefit of creditors or other marshaling of assets and liabilities of the Company referred to in Section 11.2, to receive, pursuant to and in accordance with such Section, cash, property and securities otherwise payable or deliverable to such Holder, or (2) under the conditions specified in Section 11.3, to prevent any payment prohibited by such Section or enforce their rights pursuant to Section 11.3(c).

11.6 NO WAIVER OF SUBORDINATION PROVISIONS. (a) No right of any present

or future holder of any Senior Indebtedness to enforce subordination as herein provided shall at any time in any way be prejudiced or impaired by any act or failure to act on the part of the Company or by any act or failure to act, in good faith, by any such holder, or by any non-compliance by the Company with the terms, provisions and covenants of this Agreement, regardless of any knowledge thereof any such holder may have or be otherwise charged with.

(b) Without limiting the generality of Subsection (a) of this Section 11.6, the holders of Senior Indebtedness may, at any time and from time to time, without the consent of or notice to the Holders of the Notes, without incurring responsibility to the Holders of the Notes and without impairing or releasing the subordination provided in this Article or the obligations hereunder of the Holders of the Notes to the holders of Senior Indebtedness: (1) change the manner, place or terms of payment or extend the time of payment of, or renew or alter, Senior Indebtedness or any instrument evidencing the same or any agreement under which Senior Indebtedness is outstanding; (2) sell, exchange, release or otherwise deal with any property pledged, mortgaged or otherwise securing Senior Indebtedness; (3) release any Person liable in any manner for the collection or payment of Senior Indebtedness; and (4) exercise or refrain from exercising any rights against the Company and any other Person; provided, however, that in no event shall any such actions limit the right of the Holders of the Notes to take any action to accelerate the maturity of the Notes pursuant to Article VIII of this Agreement or to pursue any rights or remedies hereunder or under applicable laws if the taking of such action does not otherwise violate the terms of this Article, subject to the rights under this Article, of the holders of Senior Indebtedness to receive the cash, property or securities receivable upon the exercise of such rights or remedies.

11.7 NOTICES. The Company shall provide the Holders with prompt notice of any event known to the Company which would prohibit the making of any payment of money to the Holders in respect of the Notes pursuant to the provisions of this Article.

11.8 RELIANCE ON JUDICIAL ORDERS OR CERTIFICATES. Upon any payment or distribution of assets of the Company referred to in this Article, the Holders of the Notes shall be entitled to rely upon any order or decree entered by any court of competent jurisdiction in which such insolvency, bankruptcy, receivership, liquidation, reorganization, dissolution, winding up or similar case or proceeding is pending, or a certificate of the trustee in bankruptcy, receiver, liquidating trustee, custodian, assignee for the benefit of creditors, agent or other person making such payment or distribution, delivered to the Holders of Notes or a certificate of a Senior Representative, for the purpose of ascertaining the Persons entitled to participate in such payment or distribution, the holders of Senior Indebtedness and other indebtedness of the Company, the amount thereof or payable thereon, the amount or amounts paid or distributed thereon and all other facts pertinent thereto or to this Article, provided that the foregoing shall apply only if such court has been fully apprised of the provisions of this Article.

11.9 NO SUSPENSION OF REMEDIES. Nothing contained in this Article shall limit the right of the Holders of Notes to take any action to accelerate the maturity of the Notes pursuant to Article VIII of this Agreement or to pursue any rights or remedies hereunder or under applicable law, subject to the rights under this Article of the holders of Senior Indebtedness to receive the cash, property or securities receivable upon the exercise of such rights or remedies.

11.10 REINSTATEMENT. The provisions of this Article shall continue to be effective or reinstated, as the case may be, if at any time any payment of the Senior Indebtedness is rescinded or must otherwise be returned by any holder of Senior Indebtedness upon the insolvency, bankruptcy or reorganization of the Company or otherwise, all as though such payment had not been made.

11.11 AMENDMENTS TO ARTICLE XI. No change, modification or amendment of any provision of this Article shall be effective against any holder of Senior Indebtedness that did not consent to such change, modification or amendment.

ARTICLE XII

REDEMPTION OF NOTES

12.1 RIGHT OF REDEMPTION. The Notes may be redeemed at the election of

the Company, as a whole or from time to time in part, at any time on or after November 1, 2002, at the Redemption Prices specified in the form of Note hereinafter set forth, together with accrued interest, if any, to the Redemption Date.

12.2 APPLICABILITY OF ARTICLE. Redemption of Notes at the election of the Company or otherwise, as permitted or required by any provision of this Agreement, shall be made in accordance with such provision and this Article.

12.3 ELECTION TO REDEEM; NOTICE TO HOLDERS. The election of the Company to redeem any Notes pursuant to Section 12.1 shall be evidenced by a Board Resolution. In case of any redemption at the election of the Company of less than all of the Notes, the Company shall, at least 30 days prior to the Redemption Date fixed by the Company, notify the Holders of such Redemption Date and of the principal amount of Notes to be redeemed.

12.4 SELECTION BY THE COMPANY OF NOTES TO BE REDEEMED. If less than all the Notes are to be redeemed, the particular Notes to be redeemed shall be selected at least 30 days and not more than 60 days prior to the Redemption Date by the Company, from the Notes not previously called for redemption, by such method as the Company shall deem fair and appropriate and which may provide for the selection for redemption of portions (equal to $ 1,000 or any integral multiple thereof) of the principal amount of Notes of a denomination larger than $1,000.

The Company shall promptly notify the Holders in writing of the Notes selected for redemption and, in the case of any Notes selected for partial redemption, the principal amount thereof to be redeemed.

For all purposes of this Agreement, unless the context otherwise requires, all provisions relating to the redemption of Notes shall relate, in the case of any Notes redeemed or to be redeemed only in part, to the portion of the principal amount of such Notes which has been or is to be redeemed.

12.5 NOTICE OF REDEMPTION. Notice of redemption shall be given by first-class mail, postage prepaid, mailed not less than 30 nor more than 60 days prior to the Redemption Date, to each Holder to be redeemed, at his address appearing in the Note Register.

All notices of redemption shall state:

(1) the Redemption Date,

(2) the Redemption Price,

(3) if less than all the Notes are to be redeemed, the identification (and, in the case of partial redemption of any Notes, the principal amounts) of the particular Notes to be redeemed,

(4) that on the Redemption Date the Redemption Price will become due and payable upon each such Note to be redeemed and that interest thereon will cease to accrue on and after said date, and

(5) the place or places where such Notes are to be surrendered for payment of the Redemption Price.

Notice of redemption of Notes to be redeemed at the election of the Company shall be given by the Company.

12.6 DEPOSIT OF REDEMPTION PRICE. On or prior to any Redemption Date, the Company shall deposit with the Paying Agent (which for purposes of this Article shall not be the Company) an amount of money sufficient to pay the Redemption Price of, and accrued interest on, all the Notes which are to be redeemed on that date.

12.7 NOTES PAYABLE ON REDEMPTION DATE. Notice of redemption having been given as aforesaid, the Notes so to be redeemed shall, on the Redemption Date,

become due and payable at the Redemption Price therein specified, and from and after such date (unless the Company shall default in the payment of the Redemption Price and accrued interest) such Notes shall cease to bear interest. Upon surrender of any such Note for redemption in accordance with said notice, such Note shall be paid by the Company at the Redemption Price, together with accrued interest, if any, to the Redemption Date.

If any Note called for redemption shall not be so paid upon surrender thereof for redemption, the principal (and premium, if any) shall, until paid, bear interest from the Redemption Date at the rate of 14% per annum.

12.8 NOTES REDEEMED IN PART. Any Note which is to be redeemed only in part shall be surrendered at an office or agency of the Company designated by the Company in its notice of redemption for that purpose (with, if the Company so requires, due endorsement by, or a written instrument of transfer in form satisfactory to the Company duly executed by, the Holder thereof or his attorney duly authorized in writing), and the Company shall execute and deliver to the Holder of such Note without service charge, a new Note or Notes, of any authorized denomination as requested by such Holder, in aggregate principal amount equal to and in exchange for the unredeemed portion of the principal of the Note so surrendered.

12.9 SURVIVAL OF WARRANTS. Notwithstanding anything to the contrary herein, in the event that the Company exercises its right to redeem the Notes as provided in this Article XII, the Warrants shall survive and shall remain in full force and effect in accordance with their terms.

ARTICLE XIII

CONSOLIDATION, MERGER, CONVEYANCE, SALE, TRANSFER OR LEASE

13.1 COMPANY MAY CONSOLIDATE, ETC., ONLY ON CERTAIN TERMS. The Company shall not consolidate with or merge into any other Person or convey, sell, transfer or lease its properties and assets substantially as an entirety to any Person, and the Company shall not permit any Person to consolidate with or merge into the Company or convey, sell, transfer or lease its properties and assets substantially as an entirety to the Company, unless:

(1) in case the Company shall consolidate with or merge into another Person or convey, sell, transfer or lease its properties and assets substantially as an entirety to any Person, the Person formed by such consolidation or into which the Company is merged or the Person which acquires by conveyance, sale or transfer, or which leases, the properties and assets of the Company substantially as an entirety shall be a corporation, partnership or trust, shall be organized and validly existing under the laws of the United States of America, any State thereof or the District of Columbia and shall expressly assume, by a counterpart to this Agreement or an agreement, executed and delivered to the Company, in form satisfactory to the Company, the due and punctual payment of the principal of (and premium, if any) and interest on all the Notes and the performance or observance of every covenant of this Agreement on the part of the Company to be performed or observed;

(2) immediately after giving effect to such transaction and treating any Debt which becomes an obligation of the Company or a Subsidiary as a result of such transaction as having been incurred by the Company or such Subsidiary at the time of such transaction, no Event of Default, and no event which, after notice or lapse of time or both, would become an Event of Default, shall have happened and be continuing;

(3) if, as a result of any such consolidation or merger or such conveyance, transfer or lease, properties or assets of the Company would become subject to a mortgage, pledge, lien, security interest or other encumbrance which would not be permitted by this Agreement, the Company or such successor corporation or Person, as the case may be, shall take such steps as shall be necessary effectively to secure the Notes (and if the Company selects, any Debt ranking pari passu with the Notes) equally and ratably with all Debt secured thereby; and

(4) the Company has delivered to the Holders an Officers' Certificate and an Opinion of Counsel, each stating that such consolidation, merger, conveyance, transfer or lease and, if a counterpart to this Agreement or an agreement is required in connection with such transaction, such counterpart or agreement complies with this Article and that all conditions precedent herein provided for relating to such transaction have been complied with.

13.2 SUCCESSOR SUBSTITUTED. Upon any consolidation of the Company with, or merger of the Company into, any other Person or any conveyance, sale, transfer or lease of the properties and assets of the Company substantially as an entirety in accordance with Section 13.1, the successor Person formed by such consolidation or into which the Company is merged or to which such conveyance, sale, transfer or lease is made shall succeed to, and be substituted for, and may exercise every right and power of, the Company under this Agreement with the same effect as if such successor Person had been named as the Company herein, and thereafter, except in the case of a lease, the predecessor Person shall be relieved of all obligations and covenants under this Agreement and the Notes.

ARTICLE XIV

MISCELLANEOUS

14.1 AMENDMENTS AND WAIVERS. This Agreement may not be changed, modified or discharged orally, nor may any waivers or consents be given orally hereunder, and every such change, modification, discharge, waiver or consent shall be in writing and, except as provided in the following sentence, signed by the Person against which enforcement thereof is sought. Subject to the subordination provisions contained in Article XI, this Agreement may be amended, and any of its restrictions or provisions may be waived, with the consent of the Company and of the Holders of not less than 51% in aggregate face amount of the Notes then outstanding, except that without the consent of the Holders of all the Notes then outstanding no amendment to or waiver under this Agreement shall extend the maturity of any Note, or reduce the rate of interest or any premium payable with respect to any Note, or amend Article V, VII, VIII or XI or reduce the proportion of the principal amount of the Notes required to consent to any waiver, consent or amendment.

14.2 COPIES TO REGULATORY BODIES. The Purchaser and each Holder that is an institutional investor may furnish copies of any financial statements and other certificates, reports or documents delivered to it pursuant to this Agreement to any regulatory body or commission to whose jurisdiction such Holder may be subject.

14.3 INTEGRATION AND SEVERABILITY. This Agreement embodies the entire agreement and understanding between the Purchasers and the Company and supersedes all prior agreements and understandings relating to the subject matter hereof. In case any one or more of the provisions contained in this Agreement or in any Security, or any application thereof, shall be invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein and therein, and any other application thereof, shall not in any way be affected or impaired thereby.

14.4 SUCCESSORS AND ASSIGNS. All covenants, agreements, statements, representations and warranties in this Agreement or any certificate delivered pursuant hereto by or on behalf of the Company or by or on behalf of the Purchaser shall bind and inure to the benefit of the respective successors and assigns of such party hereto, except where the context otherwise requires, and except that the Purchaser shall not be obligated to acquire any Security from any issuer other than the Company.

14.5 RELIANCE ON AND SURVIVAL OF VARIOUS PROVISIONS. All covenants, agreements, statements, representations and warranties made herein or in any certificate delivered pursuant hereto (i) shall be deemed to be material and to have been relied upon by the Purchaser, notwithstanding any investigation heretofore or hereafter made by any Purchaser or on such Purchaser's behalf, and (ii) shall survive the execution and delivery of the Notes and shall continue in full force and effect so long as any Note is outstanding and unpaid and thereafter as provided in Section 6.8.

14.6 VERIFICATION. The Purchaser and each other Holder shall be entitled to make such independent examinations as such person may deem reasonable, and to receive copies of all such instruments, certificates, opinions and other evidence as it may reasonably request, with respect to the transactions contemplated by this Agreement and the taking of all corporate proceedings in connection therewith and for the purpose of verifying the accuracy of any certificate which is made or required to be made pursuant to this Agreement.

14.7 NOTICES AND OTHER COMMUNICATIONS. All notices, requests, consents and other communications hereunder shall be in writing and shall be delivered, or shall be sent by certified or registered mail, return receipt requested, postage prepaid and addressed (i) if to the Purchaser at its address for communications set forth in Schedule 1 hereto or to such other address as may have been furnished to the Company by notice from the Purchaser, or (ii) if to any Holder of a Note other than the Purchaser, to its address set forth in the Note Register or to such other address as may have been furnished to the Company by notice from such Holder or (iii) if to the Company, to Isis Pharmaceuticals, Inc., 2292 Faraday Avenue, Carlsbad, California 92008, Attention Secretary, with a copy to the General Counsel, or to such other address as may have been

furnished to the Purchaser and the Holders other than the Purchaser by notice from the Company. All notices shall be deemed to have been given either at the time of the delivery thereof to any officer or employee of the person entitled to receive such notice at the address of such persons for purposes of this Section 14.7, or, if mailed, at the completion of the fifth full day following the time of such mailing thereof to such address, as the case may be. Whenever pursuant to this Agreement or any Note, notice is required to be given to any or all of the Holders, such requirement shall be satisfied if such notice is given, in the manner prescribed, to the persons last known by the Company to be Holders of such Notes, entitled to such notice, at the addresses of such persons last known to the Company.

14.8 GOVERNING LAW. This Agreement and the Notes shall be construed in accordance with and governed by the laws of the State of New York (without giving effect to the principles of conflict of laws thereof). If any action or proceeding shall be brought by the Purchaser or by any Holder in order to enforce any right or remedy under this Agreement or under any Security, the Company hereby consents and will, and the Company will cause each Subsidiary to, submit to the jurisdiction of any state or federal court of competent jurisdiction sitting within the area comprising the Southern District of New York on the date of this Agreement. Nothing contained in this section shall affect the right of any Holder of Notes to serve legal process in any other manner permitted by law or to bring any action or proceeding in the courts of any jurisdiction against the Company or to enforce a judgment obtained in the courts of any other jurisdiction.

14.9 REPRODUCTION OF DOCUMENTS. This Agreement and all documents relating to this Agreement, including, without limitation, (a) consents, waivers and modifications that may hereafter be executed, (b) documents received by any Purchaser at the closing of the purchase of the Notes (except the Notes themselves) and (c) financial statements, certificates and other information previously or hereafter furnished to the Purchaser, may be reproduced by the Purchaser by any photographic, photostatic, microfilm, microcard, miniature photographic or other similar process, and the Purchaser may destroy any original document so reproduced. The Company agrees and stipulates that any such reproduction shall be admissible in evidence as the original itself in any judicial or administrative proceeding (whether or not the original is in existence and whether or not such reproduction was made by the Purchaser in the regular course of business) and that any enlargement, facsimile or further reproduction of such reproduction shall likewise be admissible in evidence.

14.10 TABLE OF CONTENTS AND HEADINGS. The table of contents and the headings of the various subdivisions hereof are for convenience of reference only and shall in no way modify any of the terms or provisions hereof

14.11 COUNTERPARTS. This Agreement may be signed by each party hereto upon

a separate copy in which event both of said copies shall constitute a single counterpart of this Agreement. This Agreement may be executed in two or more counterparts, each of which shall be deemed an original, and it shall not be necessary in making proof of this Agreement to produce or account for more than one such counterpart.

IN WITNESS WHEREOF, the Company and the Purchaser have caused this Agreement to be executed and delivered in New York City, New York by their respective officers thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

By /s/ Stanley T. Crooke

Stanley T. Crooke
Chairman and Chief Executive Officer

By (*)

*CONFIDENTIAL TREATMENT REQUESTED

SCHEDULE1

PURCHASER AND PAYMENT INFORMATION

PURCHASER (NAME AND ADDRESS)	NOTES TO BE PURCHASED
1. (*)	$50,000 000

Registration instructions:
(*)

Delivery instructions:
(*)

Wire instructions:
(*)

Notices:
(*)

*CONFIDENTIAL TREATMENT REQUESTED

EXHIBIT A

FORM OF SENIOR SUBORDINATED DISCOUNT NOTE
ISIS PHARMACEUTICALS, INC.
14% SENIOR SUBORDINATED DISCOUNT NOTE
DUE NOVEMBER 1, 2007

$_____
Private Placement No._____ No._____

FOR VALUE RECEIVED, the undersigned, (herein called the "Company"), a

corporation organized and existing under the laws of the State of Delaware, hereby promises to pay to _____ or registered assigns, the principal sum of _____, DOLLARS ($_____), on November 1, 2007. The Company promises to pay interest on the principal amount of this Note on each Interest Payment Date, as set forth below, at the rate of 14% per annum.

Interest will be paid quarterly (to the holder of record of this Note at the close of business on the January 15, April 15, July 15 and October 15 immediately preceding the Interest Payment Date) on each Interest Payment Date, commencing on February 1, 2003; provided that, no interest shall accrue on the principal amount of this Note prior to November 1, 2002.

Interest on this Note will accrue from the most recent date to which interest has been paid or, if no interest has been paid, from November 1, 2002; provided that, if there is no existing default in the payment of interest and if a Note is authenticated between a Regular Record Date and the next succeeding Interest Payment Date, interest shall accrue from such Interest Payment Date. Interest will be computed on the basis of a 360-day year of twelve 30-day months.

The Company promises to pay interest on overdue principal of, and premium on, if any, this Note and interest on overdue installments of interest, to the extent lawful, at the rate borne by this Note plus 2% per annum.

Payments of the principal of, and the premium, if any, and interest on, this Note shall be made in lawful money of the United States of America in the manner and at the place provided in Article V of the Agreement hereinafter referred to.

This Note is one of the Company's 14% Senior Subordinated Discount Notes due November 1, 2007, limited in aggregate principal amount, at maturity, to $50,000,000

which are issued, in fully registered form, pursuant to that certain Purchase Agreement, dated as of October 24, 1997, between the Company and the purchaser listed on Schedule I thereto (said Purchase Agreement, as amended and modified from time to time, being herein called the "Agreement"). This Note is entitled to the benefits of, and is subject to the terms contained in the Agreement. The provisions of the Agreement are hereby incorporated in this Note to the same extent as if set forth at length herein.

The Company may deem and treat the person in whose name this Note is registered pursuant to Article IV of the Agreement as the holder and owner hereof for the purpose of receiving payments and for all other purposes whatsoever, notwithstanding any notations of ownership or transfers hereon and notwithstanding that this Note is overdue, and the Company shall not be affected by any notice to the contrary until presentation of this Note for registration of transfer as provided in Article IV of the Agreement. This Note may be transferred or exchanged and, if lost, stolen, damaged or destroyed, this Note may be replaced, in the manner and upon the conditions set forth in said Article IV.

This Note is registered on the books of the Company and is transferable only by surrender thereof at the office of the Company designated for notices in accordance with Section 14.7 of the Agreement duly endorsed or accompanied by a written instrument of transfer duly executed by the registered holder of this Note or its attorney duly authorized in writing. By its acceptance hereof, the holder of this Note agrees that in the absence of the registration of the Notes under the Securities Act of 1933, as amended (the "Securities Act"), it will offer, sell or otherwise transfer this Note (i) only (A) to the Company, (B) pursuant to any transaction under and meeting the requirements of Rule 144A, as amended from time to time, promulgated under the Securities Act, (C) pursuant to an exemption from registration under the Securities Act in accordance with Rule 144, as amended from time to time, promulgated under the Securities Act or (D) in accordance with any other available exemption from the registration requirements of Section 5 of the Securities Act, and (ii) in accordance with any applicable federal and state securities laws.

In certain circumstances involving the occurrence of a Change of Control or Asset Sale (each as defined in the Agreement), the Holder hereof shall have the right to require the Company to repurchase this Note in whole or in part in integral multiples of $ 1,000 of the principal, at a purchase price in cash equal to a certain percentage of the Accreted Value hereof, as set forth in Sections 7.4(a) and 7.5(b) of the Agreement, respectively, together with accrued and unpaid interest, if any, to the date of repurchase.

In case an Event of Default (as defined in the Agreement) shall happen and be continuing, the principal of this Note may become or be declared due and payable in the manner and with the effect provided in the Agreement.

This Note is subordinate to all Senior Indebtedness (as defined in the Agreement), to the extent and as provided in Article XI of the Agreement.

The Notes are subject to redemption upon not less than 30 nor more than 60 days' notice by mail, at any time on or after November 1, 2002, as a whole or in part, at the election of the Company, at a Redemption Price in cash equal to 100% of the Accreted Value hereof together in the case of any such redemption with accrued interest, if any, to the Redemption Date.

Should the indebtedness represented by this Note or any part thereof be collected in any proceeding provided for in the Agreement or be placed in the hands of attorneys for collection, the Company agrees to pay, in addition to the principal, premium, if any, and interest due and payable hereon, all costs of collecting this Note, including reasonable attorneys' fees and expenses.

This Note and the Agreement are governed and construed in accordance with the laws of the State of New York (without giving effect to the principles of conflict of laws thereof).

IN WITNESS THEREOF, ISIS PHARMACEUTICALS, INC. has caused this Note to be dated October 24, 1997 and to be executed on its behalf by its officers thereunto duly authorized in New York, New York.

ISIS PHARMACEUTICALS, INC.

By:_____
Stanley T. Crooke
Chairman and Chief Executive Officer

By:_____
B. Lynne Parshall
Executive Vice President and
Chief Financial Officer

BOND POWER

FOR VALUE RECEIVED,_____ hereby sells, assigns and

transfers unto_____ one note of the 14% Senior Subordinated Discount Notes due November 1, 2007 of Isis Pharmaceuticals, Inc. in the aggregate principal amount of $_____, for $_____,No. _____ herewith, standing in the name of Reliance Insurance Company on the books of said Company and do hereby irrevocably constitute and appoint _____ _____ attorney to transfer the said note on the books of the within named Company, with full power of substitution in the premises.

Dated:_____ __, ____ _____

Social Security or other identification number of assignee:_____ By:_____

In presence of

_____

EXHIBIT B

THIS WARRANT AND THE WARRANT SHARES REFERRED TO HEREIN HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED, AND MAY NOT BE SOLD, TRANSFERRED OR OTHERWISE DISPOSED OF EXCEPT IN COMPLIANCE WITH SUCH ACT.

No. of Shares:_____ Warrant No._____

WARRANT

To Purchase Common Stock of
ISIS PHARMACEUTICALS, INC.
Expiring November 1, 2004

THIS WARRANT CERTIFIES THAT, for value received, the registered holder hereof,
whose address is
or its registered assigns, is entitled to purchase from ISIS PHARMACEUTICALS, INC., a corporation organized and existing under the laws of Delaware, on or before 5 P.M., Eastern Time, November 1, 2004, shares of the Stock (as hereinafter defined) at the Basic Purchase Price (as hereinafter defined) in lawful money of the United States of America or as provided in Section 6.12 of the Purchase Agreement (as hereinafter defined). The number of shares of the Stock purchasable hereunder and the Basic Purchase Price therefor are subject to adjustment as hereinafter provided in Section 6.

SECTION 1. DEFINITIONS. For all purposes of this Warrant, the following terms shall have the meanings indicated and such terms shall include the singular as well as the plural:

"Basic Purchase Price" shall mean the price of $25.00 per share of the Stock, at which price the registered holder hereof may exercise this Warrant prior to any adjustments being made as provided in Section 6.

"Date of Original Delivery" shall mean the Closing Date as defined in the Purchase Agreement.

"Dilutive Basis" shall mean, with respect to any issuance or sale of the Stock (or any right or option to acquire the same or any Convertible Securities) by the Company after October 24, 1997, an amount equal to 85% of the Market Price on the date of such issuance or sale.

"Market Price" shall mean, as of the date of determination, the average of any number of days as determined in good faith by the Board of Directors, provided, however, that such number of days shall be no less than the 10 consecutive Trading Days (as hereinafter defined) nor more than the 60 consecutive Trading Days, in each case, immediately prior to such date, of either: (i) the average of the high and low sales prices of the Stock on such Trading Day on the NYSE, or (ii) if the Stock shall not on such Trading Day then be listed on the NYSE, the average of such high and low sales prices on the principal (determined by highest volume of the Stock during the month immediately preceding the month in which occurs the date as of which Market Price is being determined) national securities exchange (as defined in the Exchange Act) on which the Stock may then be listed, or (iii) if there shall have been no sales on the NYSE or such securities exchange on any such Trading Day, the average of the bid and asked prices on the NYSE or such securities exchange at the end of such Trading Day, or (iv) if the Stock shall not be so listed on any such Trading Day, the average of the representative bid and asked prices at the end of such Trading Day in the over-the-counter market as reported by the National Association of Securities Dealers Automated Quotations System ("NASDAQ") or a similar organization if NASDAQ is no longer reporting such information. If none of the foregoing categories (i), (ii), (iii) or (iv) shall be applicable, the term "Market Price" shall mean, as of any date, with respect to any share of the Stock, the greater of the fair market value per share of the Stock, determined in good faith by the Board of Directors based upon an appraisal of an investment banking or appraisal firm acceptable to the Warrantholders, or the net book value per share of the Stock.

"Public Offering" shall mean the offer and sale of shares of the Stock pursuant to a registration statement filed and made effective pursuant to the Securities Act.

"Purchase Agreement" shall mean the Purchase Agreement, dated as of October 24, 1997, as the same may be amended and modified from time to time in accordance with the provisions thereof, between the Company and the Purchaser.

"Purchase Price" shall mean, as of any date, the Basic Purchase Price, as the same has been adjusted from time to time pursuant to the provisions of Section 6.

"Registrable Securities" shall mean any Warrant Shares. As to any particular Registrable Securities once issued, such securities shall cease to be Registrable Securities when (i) a registration statement with respect to the sale of such securities shall have become effective under the Securities Act and such securities shall have been disposed of in accordance with such registration statement, (ii) such securities shall have been distributed to the public pursuant to Rule 144 (or any successor provision) under the Securities Act, (iii) such securities shall have been otherwise transferred, new certificates for them not bearing a legend restricting further transfer shall have been delivered by the Company and subsequent disposition of them shall not require registration or qualification of them under the Securities Act, or (iv) such securities shall have ceased to be outstanding.

"Registration Expenses" shall mean any and all expenses incident to performance of or compliance with Section 5, including, without limitation, (i) all Commission and stock exchange or National Association of Securities

Dealers, Inc. registration, filing fees and listing expenses, (ii) all fees and expenses of complying with securities or blue sky laws (including reasonable fees and disbursements of counsel for any underwriters in connection with blue sky qualifications of any Warrant Shares), (iii) all printing, messenger and delivery expenses, (iv) the fees and disbursements of counsel for the Company and of its independent public accountants, including the expenses of any special audits and/or "cold comfort" letters required by or incident to such performance and compliance, (v) the fees and disbursements of counsel retained in connection with such registration by the holders of a majority (by number of shares) of the Warrant Shares being registered, and (vi) any fees and disbursements of underwriters customarily paid by issuers or sellers of securities, including the fees and expenses of any special experts retained in connection with the requested registration.

"Stock" shall mean and include the Company's authorized common stock, $.001 par value per share, as constituted at October 24, 1997, and shall also include any class of the capital stock of the Company hereafter authorized which shall neither (i) be limited to a fixed sum or a percentage of par value in respect of the rights of the holders thereof to receive dividends and to participate in the distribution of assets upon the voluntary or involuntary liquidation, dissolution or winding-up of the Company, nor (ii) be subject at any time to redemption by the Company, provided, however, that except as provided in Section 6G, the Stock receivable upon exercise of any Warrant shall include

only shares of the capital stock of the Company designated as common stock on October 24, 1997, or shares of any class or classes of the capital stock of the Company resulting from any reclassification or reclassifications of such common stock which are not limited to any such fixed sum or percentage of par value and which are not subject to any such redemption.

"Transfer" as used in Section 5, shall include any disposition of any Warrants or Warrant Shares, or of any interest in either thereof, which would constitute a sale thereof within the meaning of the Securities Act.

"Warrantholders" shall mean, as of any date, the then registered holders of the Warrants and the then registered holders of the Warrant Shares.

"Warrants" shall mean all Warrants of the Company (including this Warrant) described in Section 1.1 of the Purchase Agreement, whether issued or issuable, which are identical as to terms and conditions, except as to the names and addresses of the Warrantholders thereunder and the number of shares of the Stock for which they may be exercised, and which evidence the right to purchase an aggregate of not in excess of 500,000 shares of the Stock (prior to making any adjustments of the character provided in Section 6), including all amendments thereto, and together with all Warrants issued in exchange, transfer or replacement of any thereof.

"Warrant Shares" shall mean all shares of the Stock purchased or purchasable by the registered holders of the Warrants upon the exercise thereof pursuant to Section 4 thereof.

All terms used in this Warrant which are not defined in this Section 1 have the meanings respectively set forth therefor in the Purchase Agreement or elsewhere in this Warrant.

SECTION 2. OWNERSHIP OF THIS WARRANT. The Company may deem and treat the person in whose name this Warrant is registered as the holder and owner hereof, notwithstanding any notations of ownership or writing hereon made by anyone other than the Company, for all purposes and shall not be affected by any notice to the contrary, until presentation of this Warrant for registration of transfer as provided in Section 3. The Company shall maintain, at its office in Carlsbad, California, a register for the Warrants, in which the Company shall record the name and address of the person in whose name each Warrant has been issued, as well as the name and address of each transferee and each prior owner of such Warrant. Within 5 Business Days after any Warrantholder shall by notice request the same, the Company will deliver to such Warrantholder a certificate, signed by one of its officers, listing the names and address of

every other Warrantholder, as such information appears in said register and in the stock

transfer books of the Company at the close of business on the day before such certificate is signed.

SECTION 3. EXCHANGE, TRANSFER AND REPLACEMENT. This Warrant is exchangeable, upon the surrender hereof by the registered holder to the Company at its office or agency provided for in Section 2, for new Warrants of like tenor, representing in the aggregate the right to purchase the number of shares of the Stock purchasable hereunder, each of such new Warrants to represent the right to purchase such number of shares of the Stock as shall be designated by said registered holder at the time of such surrender. This Warrant and all rights hereunder are transferable, in whole or in part, in compliance with applicable law and only upon the register provided for in Section 2, by the registered holder hereof in person or by duly authorized attorney, and a new Warrant shall be made and delivered by the Company, of the same tenor as this Warrant but registered in the name of the transferee, upon surrender of this Warrant with the Assignment Form attached hereto duly completed, at said office or agency of the Company. Upon receipt by the Company at its office or agency provided for in Section 2 of evidence reasonably satisfactory to it of the loss, theft, destruction or mutilation of this Warrant, and, in the case of loss, theft or destruction, of indemnity or security reasonably satisfactory to it, and upon surrender thereof this Warrant if mutilated, the Company will make and deliver a new Warrant of like tenor in replacement of this Warrant; provided, that, if an institutional investor having assets in excess of $ 100 million (as disclosed in its last published financial statement) shall be said registered holder, an agreement of indemnity by it shall be sufficient for all purposes of this Section 3. This Warrant shall be promptly cancelled by the Company upon the surrender hereof in connection with any exchange, transfer or replacement. The Company shall pay all taxes (other than securities transfer taxes) and all other expenses and charges payable in connection with the preparation, execution and delivery of Warrants pursuant to this Section 3.

SECTION 4. EXERCISE OF THIS WARRANT. A. Procedure for Exercise. In order to exercise this Warrant in whole or in part, the registered holder hereof shall complete the Subscription Form attached hereto, and deliver this Warrant to the Company together with cash in an amount equal to the aggregate Purchase Price of the shares of the Stock then being purchased, at its office or agency provided for in Section 2. The exercise of this Warrant shall be deemed to have been effected and the Purchase Price and the number of shares of the Stock issuable in connection with such exercise shall be determined as of the close of business on the Business Day prior to the date on which the last to be delivered of such completed Subscription Form and all other items required to be delivered in connection with such exercise by the registered holder hereof pursuant to Section 5 shall have been delivered at such office or agency. Upon receipt of such Subscription Form and other items, the Company shall, as promptly as practicable, and in any event within 5 days thereafter, execute or cause to be executed and deliver to said holder a certificate or certificates representing the aggregate number of

shares of the Stock specified in such Subscription Form. Each stock certificate so delivered shall be in such authorized denomination as may be requested by the registered holder hereof and shall be registered in the name of said holder or such other name as shall be designated by said holder, and, to the extent permitted by law, the person in whose name any such stock certificate shall be issuable upon such exercise shall be deemed to have become the holder of record of the shares represented thereby as of the time when the exercise of this Warrant with respect to such shares shall be deemed to have been effected. If this Warrant shall have been exercised only in part, the Company shall, at its

expense at the time of delivery of said stock certificate or certificates, deliver to said holder a new Warrant evidencing the rights of said holder to purchase the remaining shares of the Stock covered by this Warrant. The Company shall pay all taxes and other expenses and charges payable in connection with the preparation, execution and delivery of stock certificates pursuant to this Section 4, except that, in case such stock certificates shall be registered in a name or names other than the name of the registered holder of this Warrant, funds sufficient to pay all stock transfer taxes which shall be payable upon the execution and delivery of such stock certificate or certificates shall be paid by the registered holder hereof to the Company at the time of delivery of such stock certificates to the Company as mentioned above.

B. Transfer Restriction Legend. Each certificate representing Warrant Shares initially issued upon exercise of this Warrant, unless at the time of exercise such Warrant Shares are registered under the Securities Act, shall bear the following legend (and any additional legend required by any securities exchange on which the Warrant Shares may at the time be listed) on the face thereof:

> "The securities represented hereby have not been registered under the Securities Act of 1933, as amended, and the transfer of said securities is subject to the restrictions set forth in such Act, and no transfer of said securities shall be valid or effective unless and until the terms and conditions of such Act shall have been complied with."

Any certificate issued at any time upon transfer of, or in exchange for or replacement of, any certificate bearing such legend (except a new certificate issued upon completion of a public distribution of the securities represented thereby pursuant to a registration under the Securities Act) shall also bear such legend unless, in the opinion of counsel for the registered holder thereof, addressed and delivered to the Company and such holder, which shall be reasonably acceptable to the Company, the securities represented thereby need no longer be subject to the restrictions contained in the Securities Act.

C. Acknowledgment of Continuing Obligation. The Company will, at the time of the exercise of this Warrant, in whole or in part, upon the reasonable request of

the registered holder hereof but at the expense of the Company, acknowledge in writing its continuing obligation to said holder in respect of any rights (including, without limitation, any right to obtain registration under the Securities Act of the shares of the Stock issued upon such exercise) to which said holder shall continue to be entitled after such exercise in accordance with this Warrant, provided that the failure of said holder to make any such request shall not affect the continuing obligation of the Company to said holder in respect of such rights.

D. Character of Warrant Shares. All shares of the Stock issuable upon the exercise of this Warrant shall, when issued, be duly authorized, validly issued, fully paid and nonassessable.

SECTION 5. RESTRICTIONS ON TRANSFER. A. Restrictions in General. Notwithstanding any provisions contained in this Warrant to the contrary, this Warrant shall not be transferable and the related Warrant Shares shall not be transferable except upon the conditions specified in this Section 5, which conditions are intended, among other things, to insure compliance with the provisions of the Securities Act in respect of the transfer of this Warrant or transfer of such Warrant Shares. The registered holder of this Warrant agrees that it will not (i) transfer this Warrant prior to delivery to the Company of the opinion of the counsel referred to in, and to the effect described in, clause (1) of Section 5B, or (ii) transfer such Warrant Shares prior to delivery to the Company of the opinion of the counsel referred to in, and to the effect described in, clause (1) of Section 5B, or until registration of such Warrant Shares under the Securities Act has become effective. The registered holder of this Warrant agrees that such opinion of counsel must be reasonably satisfactory to the Company.

B. Statement of Intention to Transfer: Opinion of Counsel. The registered holder of this Warrant, by its acceptance hereof, agrees that prior to any transfer of this Warrant or any transfer of the related Warrant Shares, said holder will deliver a statement to the Company setting forth the intention of said holder's prospective transferee with respect to its retention or disposition of this Warrant or of said Warrant Shares (whichever is involved in such transfer), together with a signed copy of the opinion of said holder's counsel reasonably satisfactory to the Company as to the necessity or non-necessity for registration under the Securities Act in connection with such transfer.

(1) If, in the opinion of said holder's counsel, the proposed transfer of this Warrant or the proposed transfer of such Warrant Shares may be effected without registration under the Securities Act of this Warrant or such Warrant Shares, as the case may be, then the registered holder of this Warrant shall be entitled to transfer this Warrant or to transfer such Warrant Shares in accordance with the intended method of disposition specified in the statement delivered by said holder to the Company.

(2) Notwithstanding the foregoing provisions of this Section 5B, no opinion of any counsel need be furnished (x) in the event of any proposed transfer of this Warrant to an institutional investor who is an "accredited investor" as defined in Regulation D promulgated under the Securities Act and which transfer is otherwise exempt from the registration requirements of the Securities Act or (y) in the event of any proposed transfer of Warrant Shares in connection with a registration under the Securities Act.

C. Registration Requested by Warrantholders.

(1) At any time and from time to time after the date hereof, the Warrantholders shall have the right to request the Company to effect the registration under the Securities Act of all or part of such Warrantholders' Registrable Securities. Upon receipt by the Company of any such request, the Company shall promptly give notice of such proposed registration to all Warrantholders and thereupon shall, as expeditiously as possible, use its best efforts to effect the registration under the Securities Act of:

(i) all Registrable Securities which the Company has been requested to register pursuant to clause (1) of this Section 5C; and

(ii) all other Registrable Securities which Warrantholders have, within 20 days after the Company has given such notice, requested the Company to register;

all to the extent requisite to permit the sale or other disposition by the Warrantholders of the Registrable Securities so to be registered.

(2) If the managing underwriter of the public offering to be effected pursuant to a registration statement filed pursuant to clause (1) of this Section 5C of any Warrant shall advise the Company in writing (with a copy to each holder of Registrable Securities requesting registration) that, in its opinion, the number of securities requested to be included in such registration (including securities of the Company which are not Registrable Securities) exceeds the number which can be sold in such offering, the Company will include in such registration to the extent of the number which the Company is so advised can be sold in such offering:

(i) first, Registrable Securities requested to be included in such registration by the Warrantholders pursuant to clauses (i) and (ii) of Section 5C(1), pro rata among such holders on the basis of the number of Registrable Securities requested to be included by each; and

(ii) second, other securities of the Company proposed to be included in such registration, in accordance with the priorities, if any, then existing among the Company and the holders of such other securities.

(3) The Warrantholders requesting inclusion in a registration statement under this Section 5C and Section 5C of the other Warrants may withdraw from any requested registration pursuant to this Section 5C and Section 5C of the other Warrants by giving written notice to the Company prior to the filing date of such registration statement; provided, however, that for a period of three months after such withdrawal, such Warrantholders may not request any registration pursuant to this Section 5C and Section 5C or the other Warrants.

(4) The Company shall not be required to effect more than a total of three effective registrations under this Section 5C.

(5) The Company shall not be required to effect a registration pursuant to this Section 5C unless the offering includes Registrable Securities having a Fair Market Value of at least $4 million in the aggregate.

(6) The Company shall not be required to effect any registration within twelve months of the effective date of any other registration under this Section 5C.

D. "Piggyback" Registrations. If the Company at any time proposes to register any of its securities under the Securities Act (other than pursuant to Section 5C of any Warrant) on a registration statement on Form S-1, S-2 or S-3 or on any other form upon which may be registered securities similar to the Registrable Securities for sale to the general public except Form S-4 and Form S-8, the Company will at each such time give prompt notice to all Warrantholders of its intention to do so setting forth the date on which the Company proposes to file such registration statement, which date shall be no earlier than 30 days from the date of such notice, and advising each such Warrantholder of its right to have Registrable Securities included therein. Upon the written request of any Warrantholder given to the Company not less than 5 days prior to the proposed filing date of such registration statement set forth in such the Company' notice, the Company will use its best efforts to cause each of the Registrable Securities which the Company has been requested to register by such Warrant holder to be registered under the Securities Act. If the securities to be so registered for sale include securities to be sold for the account of the Company and to be distributed by or through a firm of underwriters of recognized standing under underwriting terms appropriate for such transaction, then the Registrable Securities shall also be included in such underwriting, provided that if, in the reasonable written opinion of the managing underwriter or underwriters, the total amount of such securities to be so registered, when added to such Registrable Securities, will exceed the maximum amount of the Company' securities which can be marketed (i) at a

price reasonably related to their then current market value, or (ii) without otherwise materially and adversely affecting the entire offering, the Company will include in such registration to the extent of the number which the Company is so advised can be sold in such offering securities determined as follows:

(1) if such registration as initially proposed by the Company was solely a primary registration of its securities:

(i) first, the securities proposed by the Company to be sold for its own account,

(ii) second, any Registrable Securities requested to be included in such registration pro rata among the holders of such Registrable Securities and the holders of such other shares of the Stock on the

basis of the number of Registrable Securities and other shares of the Stock requested to be included by each such holder, and

(iii) third, any other securities of the Company proposed to be included in such registration statement in accordance with the provisions, if any, then existing among the holders of such securities, and

(2) if such registration as initially proposed by the Company was in whole or in part requested by holders of securities of the Company, other than holders of Registrable Securities, pursuant to demand registration rights,

(i) first, such securities held by the holders initiating such registration, pro rata among the holders thereof, on the basis agreed upon by such holders and the Company,

(ii) second, Registrable Securities requested to be included in such registration pro rata among the holders of such Registrable Securities and the holders of such other shares of the Stock on the basis of the number of Registrable Securities and other shares of the Stock requested to be included by each such holder, and

(iii) third, any securities of the Company proposed to be included in such registration statement in accordance with the priorities, if any, then existing among the holders of such securities.

Each Warrantholder for the account of which any Registrable Securities shall be included in such underwriting shall agree not to sell any other Registrable Securities then held by such Warrantholder until 120 days after the effective date of such registration statement, except that such Warrantholder may sell such other Registrable Securities in private

transactions within such period to transferees who agree not to sell such securities within the remainder of such 120-day period. Any registration of Registrable Securities pursuant to this Section 5D shall have no effect on any registration pursuant to Section 5C.

E. The Company Obligations in Registration. If and whenever the Company is obligated by the provisions of this Section 5 to use its best efforts to effect the registration of any Registrable Securities under the Securities Act, as expeditiously as possible the Company will:

(1) prepare and file with the Commission, as expeditiously as possible within 60 days after the initial request from Warrantholders to register such Registrable Securities, a registration statement with respect to such Registrable Securities and use its best efforts to cause such registration statement to become effective within 120 days after such initial request and to remain effective; provided, however, that the Company shall not be required to keep such registration statement effective, or to prepare and file any amendments or supplements thereto, later than 5 P.M., Eastern Time, on the last business day of the sixth month following the date on which such registration statement becomes effective under the Securities Act or such longer period during which the Commission requires that such registration statement be kept effective with respect to any of the Registrable Securities so registered;

(2) prepare and file with the Commission such amendments and supplements to such registration statement and the prospectus used in connection therewith as may be necessary to keep such registration statement effective and to comply with provisions of the Securities Act with respect to the disposition of all Registrable Securities covered by such registration statement whenever the holders for whom such Registrable Securities are registered or are to be registered shall desire to dispose of the same, subject, however, to the proviso contained in the immediately preceding clause (1);

(3) furnish each holder for whom such Registrable Securities are registered or are to be registered such numbers of copies of each registration statement and printed prospectus, including a preliminary

prospectus and any amendments or supplements thereto, in conformity with the requirements of the Securities Act, and such other documents and information as such seller may reasonably request in order to facilitate the disposition of such Registrable Securities;

(4) use its best efforts to register or qualify the Registrable Securities covered by such registration statement under such other securities or blue Sky laws of such jurisdictions as each seller shall request, and do any and all other acts and things which may be necessary or advisable to enable such seller to consummate the disposition in such jurisdictions of such Registrable Securities guaranteed by such seller except that the Company shall not for any purpose be required to (i) qualify generally to

do business as a foreign corporation in any jurisdiction wherein it would not but for the requirements of this clause (4) be obligated to be so qualified, (ii) subject itself to taxation in any such jurisdiction or (iii) consent to general service of process in any such jurisdiction unless the Company is already subject to general service of process in such jurisdiction;

(5) furnish to the holders for whom such Registrable Securities are registered or are to be registered at the time of the disposition of such Registrable Securities by such holders a signed copy of an opinion of counsel for the Company acceptable to such holders as to such matters as such holders may request and substantially to the effect that, a registration statement covering such Registrable Securities has been filed with the Commission under the Securities Act and has been made effective by order of the Commission; said registration statement and the prospectus contained therein comply as to form in all material respects with the requirements of the Securities Act and, based upon such investigation and inquiry as said counsel deems necessary or appropriate, nothing has come to said counsel's attention which would cause it to believe that either said registration statement or said prospectus contains an untrue statement of a material fact or omits to state a material fact required to be stated therein or necessary to make the statements therein (in the case of said prospectus, in the light of the circumstances under which they were made) not misleading; said counsel knows of no legal or governmental proceedings required to be described in said prospectus which are not described as required, or of any contract or documents of a character required to be described in said registration statement or said prospectus or to be filed as an exhibit to said registration statement or to be incorporated by reference therein which is not described and filed as required; no stop order has been issued by the Commission suspending the effectiveness of such registration statement and that, to the best of such counsel's knowledge, no proceedings for the issuance of such a stop order are threatened or contemplated; and the applicable provisions of the securities or blue sky laws of each state in which the Company shall be required, pursuant to clause (4) of this Section 5E, to register or qualify such Registrable Securities, have been complied with, assuming the accuracy and completeness of the information furnished to such counsel with respect to each filing relating to such laws; it being understood that said counsel may rely, as to all factual matters and financial data treated therein, on certificates of the Company (copies of which shall be delivered to such holders), and as to all questions of the laws of each state in which the Company shall be so required to register or qualify such Registrable Securities, on the opinion of counsel from such state reasonably acceptable to such holders, copies of which shall be delivered to such holders;

(6) immediately notify each holder of Registrable Securities covered by such registration statement, at any time when a prospectus relating thereto is required to be delivered under the Securities Act, of the happening of any event as a result of which the prospectus included in such registration statement, as then in effect, includes

an untrue statement of a material fact or omits to state any material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances under which they were made, and at the request of any such seller promptly prepare and furnish to such seller a reasonable number of copies of a supplement to or an amendment of such prospectus as may be necessary so that, as thereafter delivered to the purchasers of such securities, such prospectus shall not include an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances under which they were made;

(7) advise each holder of Registrable Securities covered by such registration statement, promptly after it shall receive notice or obtain knowledge thereof, of the issuance of any stop order by the Commission suspending the effectiveness of such Registration Statement or the initiation or threatening of any proceeding for that purpose; and use its reasonable efforts to comply with all applicable rules and regulations of the Commission, and make generally available to the seller of Registrable Securities covered by such Registration Statement, earnings statements satisfying the provisions of Section 11 (a) of the Securities Act, no later than forty-five (45) days after the end of any twelve (12) month period (or ninety (90) days, if such period is a fiscal year) (a) commencing at the end of any fiscal quarter in which Securities are sold to underwriters in an underwritten offering, or (b) if not sold to underwriters in such an offering, beginning with the first day of the month of the Company's first fiscal quarter commencing after the effective date of a registration statement;

(8) permit any holder holding Registrable Securities covered by such registration statement or prospectus to withdraw their Registrable Securities from such registration statement or prospectus if such seller has informed the Company that it believes that such amendment or supplement does not comply in all material respects with the requirements of the Securities Act or the rules and regulations thereunder, after having been furnished with a copy thereof at least five (5) business days prior to the filing thereof,

(9) enter into such customary agreements (including an underwriting agreement in customary form) and take all such other actions as holders of a majority in the aggregate face amount of the Registrable Securities being sold or the underwriters retained by such sellers, if any, reasonably request in order to expedite or facilitate the disposition of such Registrable Securities, including customary opinions and indemnification;

(10) make available for inspection by any holder of Registrable Securities covered by such registration statement, any underwriter participating in any disposition pursuant to such registration statement, and any attorney, accountant or other agent

retained by any such holder or underwriter (collectively, the "Inspectors"), all financial and other records, pertinent corporate documents and properties of the Company and its subsidiaries (collectively, the "Records"), if any, as shall be reasonably necessary to enable them to exercise their due diligence responsibility, and cause the Company's and its subsidiaries' directors, officers and employees to supply all information and respond to all inquiries reasonably requested by any such Inspector in connection with such registration statement. Holders of Registrable Securities agree that Records and other information which the Company determines in good faith to be confidential, and of which determination the Inspectors and holders are so notified, shall not be disclosed by the Inspectors or the holders unless (a) the disclosure of such Records is necessary to avoid or correct a misstatement or omission in the Registration Statement or (b) the release of such Records is required pursuant to a subpoena or court order. Holders of Registrable Securities agree that they will, upon learning that disclosure of the Records is being sought in a court of competent jurisdiction or by a government agency, give prompt notice to the Company and allow the Company to undertake appropriate action to prevent disclosure of the Records deemed confidential;

(11) if requested by the managing underwriters or a holder of

Registrable Securities being sold in connection with an underwritten offering, promptly incorporate in a prospectus supplement or post-effective amendment such information as the managing underwriters and the holders of a majority in the aggregate face amount of the Registrable Securities being sold agree should be included therein relating to the plan of distribution with respect to such Registrable Securities including, without limitation, information with respect to the securities being sold to such underwriters, the purchase price being paid therefor by such underwriters and with respect to any other terms of the underwritten offering of the Registrable Securities to be sold in such offering; and make all required filings of such Prospectus supplement or post-effective amendment as soon as notified of the matters to be incorporated in such Prospectus supplement or post-effective amendment;

(12) list such Registrable Securities on any securities exchange on which the Company's Common Stock is then listed, if such Registrable Securities are not already so listed and if such listing is then permitted under the rules of such exchange, and provide a transfer agent and registrar for such Registrable Securities covered by such registration statement not later than the effective date of such registration statement; and

(13) obtain a CUSIP number for all Registrable Securities (unless already obtained) not later than the Effective Date.

C. Payment of Registration Expenses. The Company shall pay all Registration Expenses in connection with each registration pursuant to this Section 5.

D. Information from Holders. Notices and requests delivered by holders of Registrable Securities to the Company pursuant to this Section 5 shall contain such information regarding the Registrable Securities to be so registered and the intended method of disposition thereof as shall reasonably be required in connection with the action to be taken.

E. Indemnification.

(1) Indemnification by the Company. In the event of any registration under the Securities Act of any Registrable Securities pursuant to this Section 5, the Company hereby agrees to indemnify and hold harmless each holder disposing of such Registrable Securities, its respective agents, directors and officers, each other person, if any, who controls (within the meaning of the Securities Act) such holder and each other person (including underwriters) who participates in the offering of such Registrable Securities, against any losses, claims, damages or liabilities, to the extent that such losses, claims, damages or liabilities (or proceedings in respect thereof) arise out of or are based upon any untrue statement or alleged untrue statement of any material fact contained in any registration statement, on the effective date thereof, under which such Registrable Securities were registered under the Securities Act, in any preliminary prospectus or final prospectus contained therein or in any amendment or supplement to any preliminary prospectus or final prospectus (if used during the period the Company is required to keep such registration statement current in any such case), or arise out of or are based upon the omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the, statements therein not misleading, and will reimburse such holder, such agents, directors and officers and each such controlling person or participating person (including underwriters) for any legal or any other expenses reasonably incurred by such holder, such agents, directors and officers or such controlling person or participating person (including underwriters) in connection with investigating or defending any such loss, claim, damage, liability or proceeding, provided, that the Company will not be liable in any such case to the extent that any such loss, claim, damage or liability arises out of or is based upon an untrue statement or alleged untrue statement or omission or alleged omission made in such registration statement, said preliminary or final prospectus or said amendment or supplement in reliance upon and in conformity with written information furnished to the Company by an instrument duly executed by such holder or such controlling or participating person (including underwriters), as the case may be, specifically for use in the preparation of such registration statement; and provided, further, that, with respect to any untrue statement or omission or alleged untrue statement or omission made in any preliminary prospectus, the Company will not be liable to any holder to the extent that any loss, claim, damage, liability or expense results from the fact that a current

copy of the final prospectus was not sent or given to the Person asserting any such loss, claim, damage, liability or expense at or prior to the written confirmation of the sale of the Registrable Securities concerned

to such Person if it is determined that it was the responsibility of such holder to provide such Person with a current copy of the final prospectus and such current copy of the final prospectus was provided to such holder and would have cured the defect giving rise to such loss, claim, damage, liability or expense. The Company agrees to provide for contributions relating to such indemnification as shall be reasonably requested by any holder disposing of any Registrable Securities or by any such underwriter.

(2) Indemnification by Holders. Each such holder of Registrable Securities agrees to indemnify and hold harmless the Company, its respective agents, directors and officers, each other person, if any, who controls (within the meaning of the Security Act) the Company and each other person (including underwriters) who participate in the offering of such Registrable Securities, against all losses, claims, damages and liabilities to which the Company, may become subject under the Securities Act or otherwise, insofar as such losses, claims, damages or liabilities arise out of or are based upon any untrue statement of any material fact contained in any such registration statement, on the effective date thereof, under which such Registrable Securities were registered under the Securities Act, in any preliminary prospectus or final prospectus contained therein or in any amendment or supplement to any preliminary prospectus or final prospectus (if used during the period the Company is required to keep such registration statement current in any such case), or arise out of or are based upon the omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading, to the extent that any such loss, claim, damage or liability arises out of or is based upon any such statement or omission made in such registration statement, said preliminary or final prospectus or said amendment or supplement in reliance upon and in conformity with written information furnished to the Company by an instrument duly executed by such holder or such underwriter, as the case may be, and specifically stated to be for use in the preparation of such registration statement.

(3) Notices of Claims, Etc. Each indemnified party, promptly but not later than 30 days after its receipt of notice of the commencement of any action against it in respect of which indemnity may be sought from any indemnifying party or pursuant to this Section 5H, shall notify such indemnifying party in writing of the commencement thereof. In case any such action shall be brought against any indemnified party and it shall notify such indemnifying party of the commencement thereof, such indemnifying party will be entitled to participate therein and, to the extent that it may wish, to assume the defense thereof, with counsel satisfactory to such indemnified party, and such indemnified party may participate in such defense at such party's expense, and provided, further that the failure of any such indemnified party to give notice as provided herein shall not relieve such indemnifying party of its obligations under this Section 5E unless such failure to give notice shall materially adversely affect such indemnifying party in the defense of any such claim or any such litigation. With respect to any claim or

litigation being conducted by such indemnifying party, no indemnified party shall, except with the consent of such indemnifying party, consent to entry of any judgment or enter into any settlement of any claim as to which indemnity may be sought. No indemnifying party, in the defense of any such claim or litigation, shall, except with the consent of each indemnified party, consent to entry of any judgment or enter into any settlement which does not include as an unconditional term thereof the giving by the claimant or plaintiff to such indemnified party of a release from all liability in respect to such claim or litigation.

(4) Contribution. To the extent that the undertaking to indemnity, pay and hold harmless set forth in paragraphs (1) and (2) of Section 5(E) may be unenforceable because it is violative of any law or public policy, each party that would have been required to provide the indemnity shall

contribute the maximum portion which it is permitted to pay and satisfy under applicable law, to the payment and satisfaction of all indemnified liabilities incurred by each party entitled to indemnification under this Section 5(E); provided that in no event shall a holder of Registrable Securities be required to contribute an amount greater than the dollar amount of net proceeds received by such holder with respect to the sale of any Registrable Securities.

F. Exchange of Certificates. As soon as possible after the effectiveness of any registration statement under the Securities Act pursuant to this Section 5, the Company will deliver to the holder of any Warrant Shares so registered, upon demand of such holder and its delivery to the Company of a certificate or certificates representing such Warrant Shares bearing the legend set forth in Section 4B, a new certificate or certificates representing such Warrant Shares but not bearing such legend.

G. Obligations of the Holders. Each holder of Registrable Securities agrees:

(1) that upon receipt of any notice from the Company of the happening of any event of the kind described in Section 5E(6), such holder will forthwith discontinue such holder's disposition of Registrable Securities pursuant to the registration statement relating to such Registrable Securities until such holder's receipt of the copies of the supplemented or amended prospectus contemplated by Section 5E(6) and, if so directed by the Company, will use its best efforts to deliver to the Company (at the Company expense) all copies, other than permanent file copies, then in such Warrantholder's possession of the prospectus relating to such Registrable Securities current at the time of receipt of such notice, and

(2) that it will immediately notify the Company at any time when a prospectus relating to the registration of such Registrable Securities is required to be delivered under the Securities Act, of the happening of any event as a result of which information previously furnished by such holder to the Company in writing specifically

for inclusion in such prospectus contains an untrue statement of a material fact or omits to state any material fact required to be stated therein or necessary to make the statements therein not misleading in the light of the circumstances under which they were made.

H. Underwritten Registration. If any of the Registrable Securities covered by a registration pursuant to this Section 5 are to be sold in an underwritten offering, the investment banker or investment bankers and manager, or managers that will administer the offering will be selected by the holders of a majority in aggregate principal amount of such Registrable Securities included in such offering. No Person may participate in any underwritten registration hereunder unless such Person (a) agrees to sell such Person's Registrable Securities on the basis provided in any underwriting arrangements approved by the Persons entitled hereunder to approve such arrangements and (b) completes and executes all questionnaires, powers of attorney, indemnities, underwriting agreements and other documents required under the terms of such underwriting arrangements.

SECTION 6. ANTI-DILUTION PROVISIONS. A. Adjustment of Purchase Price and Number of Warrant Shares. The Purchase Price shall be subject to adjustment from time to time as hereinafter in this Section 6 provided. Upon each adjustment of the Purchase Price, except pursuant to Section 6G, the registered holder of this Warrant shall thereafter be entitled to purchase, at the Purchase Price resulting from such adjustment, the number of shares of the Stock (calculated to the nearest whole share) obtained by multiplying the Purchase Price in effect immediately prior to such adjustment by the number of shares of the Stock purchasable pursuant hereto immediately prior to such adjustment and dividing the product thereof by the Purchase Price resulting from such adjustment.

B. Purchase Price Adjustment Formulas. If and whenever after October 24, 1997, the Company shall issue or sell any shares of the Stock for a consideration per share which is less than the then effective Dilutive Basis at the time of such issue or sale, then in each such case (except when a different method of adjusting the Purchase Price is provided in Section 6D, 6E or 6F), the Purchase Price shall be forthwith changed (but only, except as otherwise

provided in Section 6C(3), if a reduction would result) to the lower of the prices (calculated to the nearest cent) determined as follows:

(1) by dividing (i) an amount equal to the sum of (a) the number of shares of the Stock outstanding and deemed (in accordance with Section 6C) to be outstanding immediately prior to such issue or sale, multiplied by the then effective Purchase Price, plus (b) the total consideration, if any, received and deemed (in accordance with Section 6C) received by the Company upon such issue or sale, by (ii) the total number of shares of the Stock outstanding and deemed (in accordance with Section 6C) outstanding immediately after such issue or sale; and

(2) by multiplying the Purchase Price in effect immediately prior to the time of such issue or sale by a fraction, the numerator of which shall be (i) the sum of (a) the number of shares of the Stock outstanding and deemed (in accordance with Section 6C) to be outstanding immediately prior to such issue or sale, multiplied by the Dilutive Basis immediately prior to such issue or sale, plus (b) the total consideration, if any, received and deemed (in accordance with Section 6C) received by the Company upon such issue or sale, divided by (ii) the total number of shares of Stock outstanding and deemed (in accordance with Section 6C) to be outstanding immediately after such issue or sale, and the denominator of which shall be the Dilutive Basis immediately prior to such issue or sale.

No adjustment of the Purchase Price, however, shall be made (i) in an amount less than one cent per share, but any such lesser adjustment shall be carried forward and shall be made at the time and together with the next subsequent adjustment which together with any subsequent adjustments so carried forward shall amount to one cent per share or more, (ii) in the event that such issuance or sale of Stock or Convertible Securities (as hereinafter defined) or rights or options to subscribe for or to purchase Stock or Convertible Securities is effected pursuant to a firm commitment underwriting, the aggregate gross proceeds of which are at least $10 million, (iii) in the event that such issuance or sale of Stock (or the grant by the Company of any rights or options to subscribe for or to purchase Stock) is to an officer, director or employee of, or consultant to, the Company pursuant to a stock option plan or stock purchase plan duly approved by the stockholders of the Company, or (iv) upon the exercise of the Company's outstanding Class A Warrants issued by the Company in 1993 to purchase 449,123 shares of its common stock.

C. Constructive Issuances of the Stock: Convertible Securities, Rights and Options. For purposes of Section 6B, the following provisions shall also be applicable:

(1) In case at any time the Company shall in any manner grant any rights or options to subscribe for or to purchase the Stock or any stock or securities convertible into or exchangeable for shares of the Stock (such convertible or exchangeable stock or securities being hereinafter called "Convertible Securities"), whether or not such rights or options or the right to convert or exchange any such Convertible Securities are immediately exercisable, and the price per share for which the Stock is issuable upon the exercise of such rights or options or upon conversion or exchange of such Convertible Securities (determined by dividing (i) the total amount, if any, received or receivable by the Company as consideration for the granting of such rights or options, plus the minimum aggregate amount of additional consideration, if any, payable to the Company upon the exercise of such rights or options, plus, in the case of any such rights or options which related to such Convertible Securities, the minimum

aggregate amount of additional consideration, if any, payable upon the issue or sale of such Convertible Securities and upon the conversion or exchange thereof, by (ii) the total maximum number of shares of the Stock issuable upon the exercise of such rights or options or upon the conversion or exchange of all such Convertible Securities issuable upon the exercise of such rights or options) shall be less than the Dilutive Basis in effect as of the time of granting such rights or options, then the total maximum number of shares of the Stock issuable upon the exercise of such rights or options or upon conversion or

exchange of the total maximum amount of such Convertible Securities issuable upon the exercise of such rights or options shall (on and after the date of the granting of such rights or options) be deemed to be outstanding and to have been issued for such price per share. Except as provided in clause (3) below, no further adjustments of the Purchase Price shall be made upon the actual issue of shares of the Stock or Convertible Securities upon exercise of such rights or options or upon the actual issue of shares of the Stock upon conversion or exchange of such Convertible Securities.

(2) In case at any time the Company shall in any manner issue or sell any Convertible Securities, whether or not the rights to exchange or convert thereunder are immediately exercisable, and the price per share for which the Stock is issuable upon such conversion or exchange (determined by dividing (i) the total amount received or receivable by the Company as consideration for the issue or sale of such Convertible Securities, plus the minimum aggregate amount of additional consideration, if any, payable to the Company upon the conversion or exchange thereof, by (ii) the total maximum number of shares of the Stock issuable upon the conversion or exchange of all such Convertible Securities) shall be less than the Dilutive Basis in effect as of the time of such issue or sale, then the total maximum number of shares of the Stock issuable upon conversion or exchange of all such Convertible Securities shall (on and after the date of the issue or sale of such Convertible Securities) be deemed to be outstanding and to have been issued for such price per share, provided, that, except as otherwise specified in clause (3) below, (a) no further adjustments of the Purchase Price shall be made upon the actual issue of the Stock upon conversion or exchange of such Convertible Securities, and (b) if any such issue or sale of such Convertible Securities is made upon exercise of any rights to subscribe for or to purchase of any option to purchase any such Convertible Securities for which adjustments of the Purchase Price have been or are to be made pursuant to other provisions of this Section 6C, no further adjustment of the Purchase Price shall be made by reason of such issue or sale.

(3) If the exercise price provided for in any right or option referred to in clause (1) of this Section 6C, or the rate at which any Convertible Securities referred to in clauses (1) and (2) of this Section 6C are convertible into or exchangeable for the Stock, shall change or a different exercise price or rate shall become effective at any time or from time to time (other than under or by reason of provisions designed to protect against dilution) then, upon such change becoming effective, the Purchase Price

then in effect hereunder shall forthwith be increased or decreased to such Purchase Price as would have obtained had the adjustments made and required to be made under this Section 6C upon the issuance of such rights or options or Convertible Securities been made upon the basis of (and the total consideration received therefor) (i) the issuance of the number of shares of the Stock theretofor actually delivered upon the exercise of such options or rights or upon the conversion or exchange of such Convertible Securities, (ii) the issuance of all of the Stock and all other rights, options and Convertible Securities issued after the issuance of such rights, options or Convertible Securities, and (iii) the original issuance at the time of such change of any such options, rights and Convertible Securities then still outstanding. On the expiration of any such option or right or the termination of any such right to convert or exchange such Convertible Securities, the Purchase Price then in effect hereunder shall forthwith be increased or decreased to such Purchase Price as would have obtained (a) had the adjustments made upon the issuance of such rights or options or such Convertible Securities been made upon the basis of the issuance of only the number of shares of the Stock theretofor actually delivered (and the total consideration received therefor) upon the exercise of such rights or options or upon the conversion or exchange of such Convertible Securities and (b) had adjustments been made on the basis of the Purchase Price as adjusted under the immediately preceding clause (a) for all issues or sales of the Stock or rights, options or Convertible Securities made after the issuance of such rights or options or such Convertible Securities. If the exercise price provided for in any right or option referred to in clause (1) of this Section 6C, or the rate at which any Convertible Securities referred to in clauses (1) and (2) of this Section 6C are convertible into or exchangeable for shares of the Stock, shall decrease at any time under or by reason of provisions with respect thereto designed to protect against dilution, then in the case of the delivery of shares of the Stock upon the exercise of any such right or option or upon conversion or exchange of any such Convertible Securities, the

Purchase Price then in effect hereunder shall forthwith be decreased to such Purchase Price as would have obtained had the adjustments made upon issuance of such right or option or such Convertible Securities been made upon the basis of the issuance of (and the total consideration received for) the shares of the Stock delivered as aforesaid.

(4) In case at any time any shares of the Stock or Convertible Securities or any rights or options to purchase any shares of the Stock or Convertible Securities shall be issued or sold for cash, the consideration received therefor shall be deemed to be the amount payable to the Company therefor, after deduction therefrom of any expenses incurred or any underwriting commissions or concessions or discounts or, in the case of a private placement thereof, reasonable finders' fees or brokerage commissions paid or allowed by the Company in connection therewith. In case any shares of the Stock or Convertible Securities or any rights or options to purchase any shares of the Stock or Convertible Securities shall be issued or sold for a consideration

other than cash, the amount of the consideration other than cash payable to the Company shall be deemed to be the fair value of such consideration as determined by the Board of Directors of the Company, after deduction therefrom of any expenses incurred or any underwriting commissions or concessions or discounts paid or allowed by the Company in connection therewith. In case any shares of the Stock or Convertible Securities or any rights or options to purchase any shares of the Stock or Convertible Securities shall be issued in connection with any merger of another corporation into the Company, the amount of consideration therefor shall be deemed to be the Fair Market Value as determined by the Board of Directors of the Company of such portion of the assets of such merged corporation as such Board shall determine to be attributable to such shares of the Stock, Convertible Securities, rights or options, as the case may be.

(5) In case at any time the Company shall take a record of the holders of the Stock for the purpose of entitling them (i) to receive a dividend or other distribution payable in shares of the Stock or in Convertible Securities, or (ii) to subscribe for or purchase shares of the Stock or Convertible Securities, then such record date shall be deemed to be the date of the issue or sale of the shares of the Stock deemed to have been issued or sold upon the declaration of such dividend or of such other distribution or the date of the granting of such right of subscription or purchase, as the case may be.

No adjustment in the Purchase Price, however, shall be made (i) in the event that such issuance or sale of Stock or Convertible Securities or rights or options to subscribe for or to purchase Stock or Convertible Securities is effected pursuant to a firm commitment underwriting, the aggregate gross proceeds of which are at least $10 million, (ii) in the event that such issuance or sale of Stock (or the grant by the Company of any rights or options to subscribe for or to purchase Stock) is to an officer, director or employee of, or consultant to, the Company pursuant to a stock option plan or stock purchase plan duly approved by the stockholders of the Company, or (iv) upon the exercise of the Company's outstanding Class A Warrants issued by the Company in 1993 to purchase 449,123 shares of its common stock.

D. Stock Dividends. In case at any time the Company shall declare a dividend or any other distribution upon the Stock of the Company which is payable in shares of the Stock, then the Purchase Price in effect immediately prior to the declaration of such dividend or distribution shall be reduced to the quotient obtained by dividing (i) the product of (a) the number of shares of the Stock outstanding and deemed (in accordance with Section 6C) to be outstanding immediately prior to such declaration, multiplied by (b) the then effective Purchase Price, by (ii) the total number of shares of the Stock outstanding and deemed (in accordance with Section 6C) to be outstanding immediately after such declaration.

E. Extraordinary Dividends and Distributions. In case at any time the Company shall declare a dividend or any other distribution upon the Stock payable otherwise than out of current earnings, retained earnings or earned surplus and otherwise than in shares of the Stock or Convertible Securities, the

Purchase Price in effect immediately prior to such declaration shall be reduced by an amount equal, in the case of a dividend or distribution in cash, to the amount thereof payable per share of the Stock or, in the case of any other dividend or distribution, to the Fair Market Value thereof per share of the Stock at the time such dividend or distribution was declared, as determined by the Board of Directors of the Company. For the purposes of the foregoing a dividend or distribution other than in cash shall be considered payable out of earnings, retained earnings or earned surplus only to the extent that such current earnings, retained earnings or earned surplus are charged an amount equal to the Fair Market Value of such dividend or distribution at the time of the declaration thereof, as determined by the Board of Directors of the Company. Such reductions shall take effect as of the date on which a record is taken for the purposes of such dividend or distribution, or, if a record is not taken, the date as of which the holders of record of the Stock entitled to such dividend or distribution are to be determined.

F. Stock Splits and Reverse Splits. In case at any time the Company shall subdivide its outstanding shares of the Stock into a greater number of shares, the Purchase Price in effect immediately prior to such subdivision shall be proportionately reduced and the number of Warrant Shares purchasable pursuant to this Warrant immediately prior to such subdivision shall be proportionately increased, and conversely, in case at any time the Company shall combine the outstanding shares of the Stock into a smaller number of shares, the Purchase Price in effect immediately prior to such combination shall be proportionately increased and the number of Warrant Shares purchasable upon the exercise of this Warrant immediately prior to such combination shall be proportionately reduced.

G. Adjustments for Consolidation, Merger, Sale of Assets, Reorganization, Etc. If at any time the Company shall be a party to any transaction (including without limitation a merger, consolidation, sale of all or substantially all of the Company, assets or a recapitalization of the Stock) in which the previously outstanding shares of the Stock shall be changed into and exchanged for different securities of the Company or changed into or exchanged for common stock or other securities of another corporation or other property (including cash) or any combination of any of the foregoing (each such transaction being hereinafter referred to as the "Transaction"; the Company (in the case of a recapitalization of the Stock) or such other corporation being hereinafter referred to as the "Acquiring Company"; and the common stock of the Acquiring Company being hereinafter referred to as the "Acquirer's Stock"), then, as a condition to the consummation of the Transaction, lawful and adequate provisions shall be made so that, upon the basis and the terms and in the manner provided in this Section 6G, each

holder of any Warrants, upon the exercise of such Warrants at any time after the consummation of the Transaction, shall be entitled to receive, in lieu of the shares of the Stock issuable upon such exercise prior to such consummation, at the election of such holder given by notice to the Company on or before the later of (i) the day on which the holders of the Stock approve the Transaction, or (ii) the thirtieth day following the date of delivery or mailing to such holder of the last proxy statement relating to the vote on the Transaction by the holders of the Stock:

(1) the stock and other securities, cash and property to which such holder would have been entitled upon the consummation of the Transaction if such holder had exercised such Warrants immediately prior thereto (subject to adjustments from and after the date of the consummation of the Transaction (the "Consummation Date") as nearly equivalent as possible to the adjustments provided for in Sections 6A and 6B and this Section 6G); or

(2) Except with respect to a Transaction in which the previously outstanding shares of the Stock shall be exchangeable for cash only, if the Acquiring Company meets the requirements set forth in this Section 6G, the number of shares of the Acquirer's Stock or, if the Acquiring Company fails to meet, but a Parent (as defined in this Section 6G) does meet, such requirements, the number of shares of such Parent's common stock (subject to adjustments from and after the Consummation Date as nearly equivalent as possible to the adjustments provided for in Section 6A and 6B and this Section 6G), determined by dividing (i) the product obtained by multiplying (a) the number of shares of the Stock to which the holder of such Warrants would have been entitled had such holder exercised such Warrant immediately prior to the

consummation of the Transaction, times (b) the greater of the Purchase Price or the Acquisition Price (as defined in this Section 6G) in effect on the date immediately preceding the Consummation Date, by (ii) the Market Value of the Acquirer's Stock on the date immediately preceding the Consummation bate.

For the purposes of this Section 6G: the term "Market Value" shall mean, for any share of common stock on any date specified herein, the last sale price on such date, or, if no sale takes place on such date, the average of the closing bid and asked prices on such date, in each case as officially reported on the NYSE or, if not so reported, on the principal national securities exchange on which such stock is listed or it not listed or admitted to trading, the average of the closing bid and asked prices of such stock in the over-the-counter market as reported by NASDAQ or a similar organization; and the term "Acquisition Price" shall mean the consideration per share to be paid for or received by the holders of the previously outstanding shares of the Stock in accordance with the terms of the Transaction, determined (x) in the case where the holders of the previously outstanding Stock received solely shares of the Acquirer's Stock in the Transaction, by multiplying the Market Value of the Acquirer's Stock as of the date immediately

preceding the Consummation Date by a fraction the numerator of which shall be the aggregate number of shares of the Acquirer's Stock to be received in the Transaction in exchange for all of the previously outstanding shares of the Stock and the denominator of which shall be the aggregate number of such previously outstanding shares of the Stock, and (y) in any other case, by dividing the aggregate fair market value (using Market Value for any shares of the Acquirer's Stock), as of the date immediately preceding the Consummation Date, of the aggregate consideration to be received by the holders of such previously outstanding shares of Stock by the number of shares of such previously outstanding Stock. The requirements referred to in clause (2) of this Section 6G with reference to the Acquiring Company or to a corporation (herein referred to as a "Parent") which directly or indirectly controls the Acquiring Company are as follows: (aa) its common stock is listed on the NYSE or a principal national securities exchange or bid and asked prices are reported with respect thereto by NASDAQ or a similar organization and such common stock continues to meet such requirements for listing thereon, (bb) it is required to file, and in each of its three fiscal years immediately preceding the Consummation Date has filed, reports with the Commission pursuant to Section 13 or 15(d) of the Exchange Act, and (cc) in the case of a Parent, such Parent is required to include the Acquiring Company in the consolidated financial statements contained in the Parent's Annual Report on Form 10-K and is not itself included in the consolidated financial statements of any other person (other than its consolidated subsidiaries). Notwithstanding anything contained in the Warrants to the contrary, the Company shall not effect any Transaction unless prior to or simultaneously with the consummation of such Transaction the survivor or successor corporation (if other than the Company) resulting from such Transaction shall (xx) assume by written instrument executed and delivered to each Warrantholder, the obligation to deliver to such Warrantholder such shares of stock, securities or assets as, in accordance with the foregoing provisions, such Warrantholder may be entitled to receive, and containing the express assumption of such successor corporation of the due and punctual performance and observance of every provision of this Warrant to be performed and observed by the Company and of all liabilities and obligations of the Company hereunder, and (yy) deliver to the Warrantholders an opinion of counsel, in form and substance reasonably satisfactory to the Warrantholders, to the effect that such written instrument has been duly authorized, executed and delivered by such successor corporation and constitutes a legal, valid and binding instrument enforceable (subject to applicable bankruptcy and other similar laws affecting the enforcement, of creditors, rights generally) against such successor corporation in accordance with its terms, and to such further effects as the Warrantholders may reasonably request.

H. Exceptions to Adjustment of Purchase Price. Anything herein to the contrary notwithstanding, the Company shall not be required to make any adjustment of the Purchase Price in the case of the issuance of the Warrants or the issuance of shares of

the Stock upon exercise of the Warrants or any adjustment of the exercise price with respect thereto.

I. Treasury Shares. The number of shares of the Stock outstanding at any time shall not include shares owned or held by or for the account of the Company, and the disposition of any such shares shall be considered an issue or sale of the Stock for the purposes of this Section 6.

J. Officers' Certificate. Upon each adjustment of the Purchase Price and upon each change in the number of shares of the Stock issuable upon the exercise of this Warrant, and in the event of any change in the rights of the holder of this Warrant by reason of other events herein set forth, then and in each such case, the Company will promptly mail to the registered holder of this Warrant an Officers' Certificate stating the adjusted Purchase Price and the new number of shares so issuable, or specifying the other shares of stock, securities or assets and the amount thereof receivable as a result of such change in rights, and setting forth in reasonable detail the method of calculation and the facts upon which such calculation is based.

K. Company to Prevent Dilution. In case at any time or from time to time conditions arise by reason of action taken by the Company, which in the opinion of its Board of Directors, are not adequately covered by the provisions of this Section 6, and which might materially and adversely affect the exercise rights of the registered holders of Warrants, the Board of Directors of the Company shall appoint a firm of independent certified public accountants of recognized national standing, which shall give their opinion upon the adjustment, if any, on a basis consistent with the standards established in the other provisions of this Section 6, necessary with respect to the Purchase Price, so as to preserve, without dilution, the exercise rights of the registered holders of the Warrants. Upon receipt of such opinion, the Board of Directors of the Company shall forthwith make the adjustments described therein.

SECTION 7. OPTIONAL REDUCTION OF THE PURCHASE PRICE. The Company shall have the right, at any time or from time to time, at its election, to reduce pro rata, the Purchase Price then in effect under all the Warrants then outstanding for such period or periods of time as the Board of Directors of the Company may determine. In each such case, the Company shall deliver to all Warrantholders a certificate of an officer of the Company stating (i) the election of the Company to reduce the Purchase Price in accordance with this Section 7, specifying the Purchase Price so reduced, (ii) that such election is irrevocable during the period below referred to, and (iii) the period in which such reduced Purchase Price shall be in effect, which period shall commence not less than 30 days after such certificate is delivered to the Warrantholders. Failure to receive such certificate, or any defect therein, shall not affect the validity of the reduction of the Purchase Price during such period. No reduction of the Purchase Price

pursuant to the provisions of this Section 7 shall be deemed for the purposes of Section 6 to alter or adjust the Purchase Price or to increase the number of shares then purchasable upon the exercise of the Warrants.

SECTION 8. SPECIAL AGREEMENTS OF THE COMPANY. The Company covenants and agrees that:

A. Will Reserve Shares. The Company will authorize, reserve and set apart and have available for issuance at all times, free from preemptive rights, including, without limitation, rights derived from rights offerings, that number of shares of the Stock which is deliverable upon the exercise of the Warrants, and the Company will have at all times any other rights or privileges provided for therein sufficient to enable it at any time to fulfill all its obligations hereunder.

B. Will Avoid Certain Actions. The Company will not, by amendment of its certificate of incorporation or through any reorganization, transfer of assets, consolidation, merger, issue or sale of securities or otherwise, avoid or take any action which would have the effect of avoiding the observance or performance of any of the terms to be observed or performed hereunder by the Company, but will at all times in good faith assist in carrying out all of the provisions of this Warrant and in taking all such action as may be necessary or appropriate in order to protect the rights of the registered holders of this Warrant against dilution or other impairment, and in particular, will not permit

the par value, if any, of any share of the Stock, to be or become greater than the then effective Purchase Price.

C. Will Secure Government Approvals. If any shares of the Stock required to be reserved for the purposes of exercise of this Warrant require registration with or approval of any governmental authority under any federal law (other than the Securities Act) or under any state law before such shares may be issued upon exercise of this Warrant, the Company will, at its expense, as expeditiously as possible use its best effort to cause such shares to be duly registered or approved, as the case may be.

D. Will List on Securities Exchange and NASDAQ. At any time when any of the Stock is registered under the Exchange Act, the Company will, at its expense, obtain and maintain the approval for listing in any national securities exchange (as defined in the Exchange Act) or NASDAQ upon official notice of issuance of any shares of the Stock receivable upon the exercise of the Warrants at the time outstanding and maintain the listing of such shares after their issuance; and the Company will so list on such national securities exchange or NASDAQ, as the case may be, will register under the Exchange Act (and any similar state statute then in effect), and will maintain such listing of, any other securities that at any time are issuable upon exercise of the Warrants, if and

at the time that any securities of the Company have been registered under the Exchange Act.

E. Will Enter into Separate Warrant Agreement. Prior to any disposition of Warrants, the Company will, if requested by the Warrantholders so disposing of such Warrants, execute and deliver to a bank or trust company selected by the Company and satisfactory to such Warrantholders, as Warrant Agent (herein called the "Warrant Agent"), a separate Warrant agreement in form and substance reasonably satisfactory to such Warrantholders, providing for the issuance of Warrants upon countersignature by the Warrant Agent and for the registration, transfer, exchange and exercise of Warrants, and containing the substance of the terms and provisions of the respective Warrants and all customary formal provisions in agreements of that kind. Thereafter any Warrant may be exchanged for a Warrant or Warrants issued under said separate Warrant agreement evidencing the same rights as the Warrants surrendered for exchange and thereafter any reference in Section 5 hereof to "this Warrant," "Warrants," "Warrant" or any similar term shall be deemed to include the Warrants so issued under such separate Warrant agreement. The Company shall pay all costs and expenses in connection with the execution, delivery and performance of such separate Warrant agreement, including, without limitation, the fees and expenses of the Warrant Agent.

G. Will Bind Successors. This Warrant will be binding upon any corporation succeeding to the Company by merger, consolidation of acquisition of all or substantially all of the Company's assets.

H. Will Furnish Information. Promptly upon their becoming available, the Company will deliver to each Warrantholder all reports, proxy statements and financial statements delivered or sent by the Company to its stockholders.

SECTION 9. NOTIFICATION BY THE COMPANY. In case at any time:

(1). the Company shall declare upon the Stock any dividend or other distribution (other than cash dividends which are less than an amount per share than the most recent cash dividend, if any) to the holders of the Stock;

(2) the Company shall make an offer for subscription pro rata to the Stock of any additional shares of stock of any class or other rights;

(3) the Board of Directors of the Company shall authorize (whether definitively or subject to any conditions) any capital reorganization, or reclassification of the capital stock of the Company, or consolidation or merger of the Company with, or sale of all or substantially all of its assets to, another person;

(4) the Board of Directors of the Company shall authorize (whether definitively or subject to any conditions) a voluntary dissolution, liquidation or winding-up of the Company; or

(5) the Company shall become subject to involuntary dissolution, liquidation or winding-up;

then, in any one or more of such cases, the Company shall give notice to the registered holder of this Warrant of the date on which (i) the books of the Company shall close or a record shall be taken for such dividend, distribution or subscription rights, or (ii) such reorganization, reclassification, consolidation, merger, sale, dissolution, liquidation or winding-up shall take place or be voted upon by stockholders of the Company, as the case may be. Such notice shall also specify the date as of which the holders of record of the Stock shall participate in such dividend, distribution or subscription rights, or shall be entitled to exchange their Stock or securities for other property deliverable upon such reorganization, reclassification, consolidation, merger, sale, dissolution, liquidation or winding-up, as the case may be. Such notice shall be given not less than 30 and not more than 90 days prior to the action in question and not less than 30 and not more than 90 days prior to the record date or the date on which the Company, transfer books are closed in respect thereto and such notice shall state that the action in question or the record date is subject to the effectiveness of a registration statement under the Securities Act, or to a favorable vote of stockholders, if either is required.

SECTION 1O. NOTICES. All notices requested and other communications required or permitted to be given or delivered to Warrantholders shall be in writing, and shall be delivered or shall be sent by certified or registered mail, postage prepaid and addressed, to each Warrantholder at the address shown on such Warrantholder's Warrant or Warrant Shares, or at such other address as shall have been furnished to the Company by notice from such Warrantholder. All notices, requests and other communications required or permitted to be given or delivered to the Company shall be in writing, and shall be delivered, or shall be sent by certified or registered mail, postage prepaid and addressed, to the office of the Company, at Isis Pharmaceuticals, Inc., 2292 Faraday Avenue, Carlsbad, California 92008, Attention: Secretary, or at such other address as shall have been furnished to the Warrantholders by notice from the Company. Unless otherwise indicated herein, all notices shall be deemed to be given either at the time of the delivery thereof to any officer or employee of such person entitled to receive such notice at the address of such person for purposes of this Section 10, or, if mailed at the completion of the fifth full day following the time of such mailing thereof to such address, as the case may be.

SECTION 11 - NO RIGHTS OR LIABILITIES AS SHAREHOLDER. This Warrant shall not entitle any holder hereof to any of the rights of a shareholder of the

Company. No provision hereof, in the absence of affirmative action by the holder hereof to purchase shares of the Stock, and no mere enumeration herein of the rights or privileges of the holder hereof, shall give rise to any liability of such holder for the Purchase Price or as a shareholder of the Company, whether such liability is asserted by the Company or by creditors of the Company.

SECTION 12. GOVERNING LAW; CONSENT TO JURISDICTION. This Warrant shall be governed by, and construed in accordance with, the laws of the State of New York (without giving effect to the conflict of laws principles thereof). If any action or proceeding shall be brought by any holder of this Warrant in order to enforce any right or obligations in respect of this Warrant, the Company hereby consents and will submit to the jurisdiction of any state or federal court of competent jurisdiction sitting within the area comprising the Southern District of New York on the date of this Warrant.

SECTION 13. MISCELLANEOUS. This Warrant and any provision hereof may be changed, waived, discharged or terminated only by an instrument in writing signed by the party (or any predecessor in interest thereof) against which enforcement of the same is sought. The headings in this Warrant are for purposes of reference only and shall not affect the meaning or construction of any of the

provisions hereof

IN WITNESS WHEREOF, ISIS PHARMACEUTICALS, INC. has caused this Warrant to be signed and delivered in New York City by its duly authorized officer under its corporate seal, attested by its duly authorized officer, and to be dated as of October 24, 1997.

ISIS PHARMACEUTICALS, INC.

By _____
Stanley T. Crooke
Chairman and Chief Executive Officer

[Corporate Seal]

Attest:

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

ASSIGNMENT FORM

To Be Executed by the Registered Holder
Desiring to Transfer the Within Warrant of

ISIS PHARMACEUTICALS, INC.

FOR VALUE RECEIVED, the undersigned registered holder hereby sells, assigns and transfers unto the right to purchase shares of the Stock covered by the within Warrant, and does hereby irrevocably constitute and appoint Attorney to transfer the said Warrant on the books of the Company (as defined in said Warrant), with full power of substitution.

Name of Registered Holder _____

Signature _____

Title _____

Address _____

_____

Dated;

In the presence of

_____

NOTICE:

The signature to the foregoing Assignment Form must correspond to the name as written upon the face of the within Warrant in every particular, without alteration or enlargement or any change whatsoever.

SUBSCRIPTION FORM

To Be Executed by the Registered Holder
Desiring to Exercise the Within Warrant of

ISIS PHARMACEUTICALS, INC.

The undersigned registered holder hereby exercises the right to purchase shares of the Stock covered by the within Warrant, according to the conditions thereof, and herewith makes payment in full of the Purchase Price of such shares, $.

Name of Registered Holder _____

Signature _____

Title _____

Address _____

_____

Dated; ,

EXHIBIT 10.20

CONFIDENTIAL TREATMENT REQUESTED
UNDER 17 C.F.R. SECTIONS 200.80(b)(4). 200.83
AND 240.24b-2. * INDICATES OMITTED
MATERIAL THAT IS THE SUBJECT OF A
CONFIDENTIAL TREATMENT REQUEST THAT IS
FILED SEPARATELY WITH THE COMMISSION.

ASSET PURCHASE AGREEMENT

This agreement (hereinafter, "Agreement"), effective as of December 19, 1997 (the "Effective Date"), is made by and between the following parties (which are collectively referred to in this Agreement as the "Parties"):

GEN-PROBE INCORPORATED, a Delaware Corporation, having a principal place of business at 10210 Genetic Center Drive, San Diego, CA 92121, U.S.A (hereinafter "Gen-Probe"); and

ISIS PHARMACEUTICALS, INC., a Delaware Corporation, having a principal place of business at Carlsbad Research Center, 2292 Faraday Avenue, Carlsbad, California 92008 (hereinafter "Isis")

RECITALS

WHEREAS, Gen-Probe has decided to exit its business related to the research, development and production of phosphorothioate oligonucleotides as antisense therapeutic agents; and

WHEREAS, Isis has agreed to acquire from Gen-Probe, and Gen-Probe has agreed to sell to Isis, substantially all of such business;

NOW, THEREFORE, in consideration of the foregoing premises, mutual covenants and promises set forth herein and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the Parties agree as follows:

ARTICLE I
DEFINITIONS

For the purposes of this Agreement, the following words and phrases shall have the following meanings set forth in this Article I unless the context otherwise requires. Words in the singular shall include the plural and vice versa.

1.1 "Acquired Assets" shall mean all right, title and interest in and to the assets listed on Schedule A attached hereto.

1.2 "Acquired Business" shall mean, collectively, the Acquired Assets and the Assumed Liabilities, which together represent substantially all the business of Gen-Probe related to the Transferred Products.

1.3 "Affiliate" shall mean, with respect to any Person, any other Person which directly or indirectly controls, is controlled by, or is under common control with, such Person. A Person shall be regarded as in control of another Person if it

owns, or directly or indirectly controls, more than fifty percent (50%) of the voting stock or other ownership interest of the other Person, or if it directly or indirectly possesses the power to direct or cause the direction of the management and policies of the other Person by any means whatsoever.

1.4 "Assumed Liabilities" shall mean all liabilities and obligations with respect to the Acquired Assets which accrue or arise from and after the Closing, including without limitation all liabilities and obligations under the NTIS Agreements and the other agreements included within the Acquired Assets.

1.5 "Calendar Half Year" shall mean, for each calendar year, the six months

ending June 30th and December 31st of such year, without regard to whether such dates are otherwise business days.

1.6 "Calendar Year" shall mean any calendar year commencing on January 1 and ending on December 31; provided, however, that the 1997 Calendar Year shall be the period commencing on the date hereof and ending on December 31, 1997.

1.7 "Closing" shall have the meaning set forth in Section 2.5 below.

1.8 "Collaborative Partner" shall mean, with respect to Isis, any Third Party that is a party to any drug discovery, development or commercialization collaboration agreement or arrangement with Isis.

1.9 "Exchange Rate" shall mean, with respect to any amount to be converted from a foreign currency to U.S. Dollars hereunder, at the conversion rate existing in the United States (as reported in the Wall Street Journal) on the last working day of the Calendar Half Year preceding the applicable Calendar Half Year. Such payments shall be without deduction of exchange, collection, or other charges.

1.10 "Field" shall mean the research, development, production, marketing, and distribution of phosphorothioate oligonucleotides as antisense therapeutic agents.

1.11 "First Commercial Sale" shall mean the initial transfer by Isis of a Transferred Product for value to a Third Party and not for demonstration, certification, testing or promotional purposes.

1.12 "Gen-Probe Licensed Patents" shall mean the patents and patent applications set forth in Exhibit D, which is hereby incorporated by reference into this Agreement, together with all patents, foreign and domestic, that have issued or in the future issue therefrom, including utility, model and design patents and certificates of invention; and all divisionals, continuations, continuations-in-part, reissues, renewals, re-examination, extensions or additions to any such patents

and patent applications; all to the extent and only to the extent that Gen-Probe has the right to grant licenses, immunities or other rights thereunder as of the date of this Agreement.

1.13 "Gen-Probe Net Sales" shall mean that portion of the Net Sales that is attributable to Gen-Probe Products of the amount billed or invoiced on sales of any Transferred Products sold in or made in the territory, with no deduction for corporate taxes and/or franchise or corporate income taxes, (for any Transferred Product transferred for consideration other than cash, except Gen-Probe Products transferred for research, clinical trials, compassionate use programs or marketing samples, the sales price shall be deemed to be the average price at which identical Transferred Products were sold by Isis, its sublicensees, Collaborative Partners or its Affiliates in such country during such Calendar Half Year in "arms-length" transactions) less:

(a) Customary trade, quantity or cash discounts and nonaffiliated brokers' or agents' commissions actually allowed and taken;

(b) Amounts repaid or credited by reason of rejections, recalls or returns;

(c) Any freight or other transportation costs, insurance charges, duties, tariffs and all sales and excise taxes and other governmental charges based directly on sales or turnover or delivery of material produced under this Agreement.

1.14 "Gen-Probe Product" shall mean a product in the Field that falls within the scope of one or more Valid Claims of the Gen-Probe Licensed Patents.

1.15 "NTIS Agreements" shall mean, collectively, the following three agreements, appended hereto as exhibits and hereby made a part of this Agreement:

(a) the Settlement Agreement dated on or about October 17, 1995 among the Public Health Service, Lynx Therapeutics, Inc.,

Genta, Inc., and Gen-Probe (attached hereto as Exhibit A);

(b) the Amended License Agreement dated on or about October 17, 1995 between the Public Health Service and Gen-Probe (attached hereto as Exhibit B); and

(c) the Second License Amendment dated on or about July 24, 1996 between the Public Health Service and Gen-Probe (attached hereto as Exhibit C).

1.16 "NTIS Licensed Patents" shall mean:

(a) U.S. patent applications and patents listed in Exhibit E, all divisions and continuations of these applications, all patents issuing from such

applications, divisions, and continuations, and any reissues, reexaminations, and extensions of all such patents;

(b) to the extent that the following contain one or more claims directed to the invention or inventions disclosed in (a) above: i) continuations-in-part of (a) above; ii) all divisions and continuations of these continuations-in-part, divisions, and continuations; iii) all patents issuing from such continuations-in-part, divisions, and continuations; and iv) any reissues, reexaminations, and extensions of all such patents;

(c) to the extent that the following contain one or more claims directed to the invention or inventions disclosed in (a) above: all counterpart foreign applications and patents to (a) and (b) above, including those listed in Exhibit D.

NTIS Licensed Patents shall also include (b) or (c) above to the extent that they contain one or more claims directed to new matter which is not subject matter disclosed in (a) above.

1.17 "NTIS Product" shall mean a phosphorothioate oligodeoxyribonucleotide composition and a carrier, or any other substance or composition of matter, encompassed within the scope of a claim in a patent within the NTIS Licensed Patents.

1.18 "Net Sales" shall mean the amount billed or invoiced on sales of any NTIS Products sold in or made in the Territory, with no deduction for corporate taxes and/or franchise or corporate income taxes, (for any NTIS Product transferred for consideration other than cash, except NTIS Product transferred for research, clinical trials, compassionate use programs or marketing samples, the sales price shall be deemed to be the average price at which identical NTIS Product were sold by Isis, its sublicensees, Collaborative Partners or its Affiliates in such country during such Calendar Half Year in "arms-length" transactions) less:

(a) Customary trade, quantity or cash discounts and nonaffiliated brokers' or agents' commissions actually allowed and taken;

(b) Amounts repaid or credited by reason of rejections, recalls or returns;

(c) Any freight or other transportation costs, insurance charges, duties, tariffs and all sales and excise taxes and other governmental charges based directly on sales or turnover or delivery of material produced under this Agreement.

1.19 "Person" shall mean an individual, corporation, limited liability company, partnership, trust, business trust, association, joint stock company, joint venture,

pool, syndicate, sole proprietorship, unincorporated organization, governmental authority or any other form of entity not specifically listed herein.

1.20 "Territory" shall mean all countries in which an NTIS Licensed Patent or a

Gen-Probe Licensed Patent subsists.

1.21 "Third Party" shall mean, with respect to a Party, any corporation or other business entity that is not an Affiliate of such Party.

1.22 "Transferred Products" shall mean, collectively, NTIS Products and GenProbe Products.

1.23 "U.S. Dollar" shall mean the United States dollar.

1.24 "Valid Patent Claim" shall mean either: (a) a claim of an issued and unexpired patent included within the Gen-Probe Licensed Patents, which has not been held permanently revoked, unenforceable or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, and which has not been admitted to be invalid or unenforceable through reissue or disclaimer or otherwise; or (b) a claim of a pending patent application included within the Gen-Probe Licensed Patents, which claim was filed in good faith and has not been abandoned or finally disallowed without the possibility of appeal or refiling of such application.

ARTICLE 11
THE TRANSACTION

2.1 Purchase and Sale of Assets. On and subject to the terms and conditions of this Agreement, Isis agrees to purchase from Gen-Probe, and Gen-Probe agrees to sell, transfer, convey, assign and deliver to Isis, all of the Acquired Assets at the Closing for the consideration specified below in Article IV.

2.2 Assumption of Liabilities. On and subject to the terms and conditions of this Agreement, Isis agrees to assume and fully discharge in a due and timely manner all of the Assumed Liabilities from and after the Closing. Isis will not assume or have any responsibility, however, with respect to any other obligation or liability of Gen-Probe not included within the definition of Assumed Liabilities

2.3 Cooperation. Gen-Probe and Isis shall cooperate to obtain all necessary or appropriate NIH approvals respecting the assignment set forth in this Article II.

2.4 Warranties.

2.4.1 Gen-Probe warrants that the NTIS Agreements and licenses are current and in good standing, including but not limited to, full payment of all fees and other monetary obligations up to and including December 31, 1997.

2.4.2 Gen-Probe warrants that it is transferring all of its right and interests in the NTIS Agreements.

2.5 Closing. The closing of the transactions contemplated by this Agreement (the "Closing") shall take place on or about December 19, 1997, but in no event later than December 29, 1997.

ARTICLE III
GRANT

3.1 License Grant. Subject to the terms and conditions set forth herein, at the Closing, Gen-Probe shall grant to Isis and its Affiliates an exclusive, perpetual license within the Field to the Gen-Probe Licensed Patents, to make, have made, use, import, have sold and sell Gen-Probe Products.

3.2 Limitation of Rights. Isis acknowledges that its rights under Gen-Probe Licensed Patents are limited to those expressly granted herein and that Isis is not granted the right to sell, transfer, or otherwise make available to Third Parties the Gen-Probe Licensed Patents or any products other than Gen-Probe Products.

3.3 Sublicensing. The license rights granted by Gen-Probe to Isis under this Article III may be sublicensed by Isis only with the prior written consent of Gen-Probe, which consent shall not be unreasonably withheld, and only to its Affiliates, Collaborative Partners or suppliers (subject to all of the

limitations and restrictions contained herein) in connection with the development, design or supply of products, components or materials to Isis or its Affiliates for or in connection with the activities licensed under this Article 3.

ARTICLE IV
CONSIDERATION

As consideration for the sale of the Acquired Business and the license to the Gen-Probe Licensed Patents granted herein, Isis agrees:

(1) to pay Gen-Probe (*) at the Closing, contingent upon receiving no objections to the sale from NTIS, NIH, Public Health Service and/or any other government agency before Closing.

(2) to pay Gen-Probe further contingent consideration equal to (*) made by Isis and/or its Affiliates, Collaborative Partners and sublicensees; and,

*CONFIDENTIAL TREATMENT REQUESTED

7

(3) to pay Gen-Probe further contingent consideration equal to (*) made by Isis, and/or its Affiliates, Collaborative Partners, and its permitted sublicensees.

By way of example and for avoidance of doubt, the highest contingent consideration Gen-Probe could receive is 2% if a product used both NTIS Licensed Patents and the Gen-Probe Licensed Patents.

ARTICLE V
REPORTS AND ACCOUNTING

5.1 Records. During the term of this Agreement, Isis shall keep, and cause its Affiliates and permitted licensees and sublicensees to keep, complete and accurate records in sufficient detail to property reflect all gross sales, Net Sales, and Gen-Probe Net Sales and to enable the contingent consideration payable hereunder to be determined. Such records shall be maintained for at least thirty-six (36) months after the payment to which the records apply has been made.

5.2 Reports. Isis agrees to submit to Gen-Probe, within sixty (60) days after each Calendar Half Year ending June 30th and December 31st, reports setting forth for the preceding six (6) month period the amount of Transferred Product sold or otherwise disposed of (except Transferred Product scrapped prior to shipment from its place of manufacture) for value by Isis and its included Affiliates, Collaborative Partners, licensees and sublicensees in the Territory, the Net Sales and Gen-Probe Net Sales thereof, and the amount of contingent consideration due thereon; and with each such report, Isis agrees to pay the amount of such contingent consideration due. If no such contingent consideration is due to Gen-Probe for any report period, the written report shall so state.

5.3 Audits.

5.3.1 Upon the written request of Gen-Probe and not more than once in each Calendar Year, Isis shall permit an independent certified public accounting firm, selected by Gen-Probe, at Gen-Probe's expense, to have access during normal business hours to such of the records of Isis as may be reasonably necessary to verify the accuracy of the contingent consideration reports hereunder for any year ending not more than thirty-six (36) months prior to the date of such request.

5.3.2. If such accounting firm concludes that additional contingent consideration was owed during such period, Isis shall pay the additional contingent consideration within thirty (30) days of the date Gen-Probe delivers to Isis such accounting firm's written report so concluding. The fees charged by such accounting firm shall be paid by Gen-Probe; provided, however, that if any

audit performed under this Section reveals an underpayment in excess of five percent (5%) in any Calendar Half Year, Isis shall bear the full cost of such audit.

5.3.3 Isis shall include in each sublicense of the Gen-Probe Licensed Patents and the NTIS Patents granted by it pursuant to this Agreement, a provision requiring the sublicensee, to make reports to Isis and to keep and maintain records of sales made pursuant to such sublicense. Isis shall grant Gen-Probe's accountant access to all sublicensee records maintained by Isis pursuant to Section 5.3.1.

5.4 Confidential Financial Information. Gen-Probe shall treat all financial information subject to review under this Article V or under any sublicense agreement as confidential, and shall require its accounting firm to retain all such financial information in confidence.

ARTICLE VI
PAYMENTS

6.1 Payment Terms. Contingent consideration shown to have accrued by each report provided for under Article V above shall be due and payable on the date such report is due. Payment of contingent consideration in whole or in part may be made in advance of such due date.

6.2 Payment Method. Except as provided in this Section 6.2, all payments by Isis to Gen-Probe under this Agreement shall be paid in U. S. Dollars at the Exchange Rate, and all such payments shall be originated from a United States bank located in the United States and made by bank wire transfer in immediately available funds to such account as Gen-Probe shall designate before such payment is due. Upon Gen-Probe's election made in writing not less than thirty (30) days prior to any payment date, Isis shall pay all contingent consideration owing to Gen-Probe hereunder in the currency in which such contingent consideration accrued, without conversion into U. S. Dollars.

6.3 Exchange Control. If at any time legal restrictions prevent the prompt remittance of part or all contingent consideration with respect to any country where the Transferred Products are sold, payment shall be made through such lawful means or methods as Gen-Probe reasonably shall determine.

6.4 Late Payments. Any payments by Isis that are not paid on or before the date such payments are due under this Agreement shall bear interest, to the extent permitted by law, at an annual rate of two percentage points above the annual prime rate of interest most recently declared by Wells Fargo Bank (or its successor), calculated based on the number of days that payment is delinquent.

ARTICLE VII
CONFIDENTIALITY

Gen-Probe and Isis shall not disclose, except as required elsewhere in this Agreement, any terms or conditions of this Agreement to any Third Party without the prior consent of the other party. Notwithstanding the foregoing, within thirty (30) days after execution of the Agreement, Isis and Gen-Probe shall agree upon the substance of information that can be used to describe the terms of this transaction and the timing of any release of said agreed upon information, and Isis and Gen-Probe may disclose such information only in conformance with this agreed upon timing and substance.

ARTICLE VIII
PATENTS AND PATENT APPLICATIONS

8.1 Prosecution and Maintenance. Gen-Probe shall be responsible for and shall control, at its sole discretion and expense, the preparation, filing, prosecution, defense and maintenance of all patents and patent applications included in the Gen-Probe Licensed Patents. Gen-Probe shall be under no obligation to prosecute, defend and/or maintain any of the Gen-Probe Licensed Patents. Should Gen-Probe elect not to prosecute, defend and/or maintain any Gen-Probe Licensed Patent for which Isis has been granted an exclusive license

under Article III herein, Gen-Probe shall provide Isis with sixty (60) days notice of such decision and Isis shall have the right, with notification in writing to GenProbe within thirty (30) days of receiving Gen-Probe's notice, to choose to defend, prosecute and/or maintain such Gen-Probe Licensed Patents at Isis's sole expense. Gen-Probe agrees to cooperate with Isis in such action. If Isis does not respond within thirty (30) days, Gen-Probe shall have no further obligation or duty with regard to the subject patents.

8.2 Notification of Infringement. Isis shall notify Gen-Probe, within two (2) weeks of Isis receiving notification or knowledge, of any infringement known to Isis of the Gen-Probe Licensed Patents and shall provide Gen-Probe with the available evidence, if any, of such infringement.

8.3 Enforcement of Patent Rights. Gen-Probe, at its sole expense, shall have the right to determine the appropriate course of action to enforce the Gen-Probe Licensed Patents or otherwise abate the infringement thereof, to take (or refrain from taking) appropriate action to enforce the Gen-Probe Licensed Patents, to control any litigation or other enforcement action and to enter into, or permit, the settlement of any such litigation or other enforcement action with respect to the Gen-Probe Licensed Patents. Isis shall fully cooperate with Gen-Probe in the planning and execution of any action to enforce the Gen-Probe Licensed Patents. Should Gen-Probe elect not to take action to enforce the Gen-Probe Licensed Patents or otherwise abate the infringement thereof, Gen-Probe shall provide Isis with notice of such decision within sixty (60) days of such decision,

and then Isis shall, at its sole expense, have the right to enforce the Gen-Probe Licensed Patents as Isis determines is appropriate, provided, however, that all pleadings, discovery, motion practice and responses thereto relating to the construction of patent claims, or application of prior art thereto, shall be submitted to Gen-Probe for its review and timely approval before being filed in any such action or proceeding and, provided further, that Isis shall keep Gen-Probe reasonably informed of developments in such action or proceeding.

ARTICLE IX
DISCLAIMER OF WARRANTIES

9.1 THE NTIS LICENSED PATENTS AND THE GEN-PROBE LICENSED PATENTS, TO THE EXTENT LICENSED HEREUNDER, ARE PROVIDED ON AN "AS IS" BASIS AND GEN-PROBE MAKES NO REPRESENTATIONS OR WARRANTIES, EXPRESS OR IMPLIED, OTHER THAN THOSE WARRANTIES WHICH APPEAR IN SECTION 2.4, WITH RESPECT THERETO. BY WAY OF EXAMPLE BUT NOT OF LIMITATION, GEN-PROBE MAKES NO REPRESENTATIONS OR WARRANTIES:

(a) OF COMMERCIAL UTILITY;

(b) OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE;

(c) OF THE VALIDITY OR SCOPE OF ANY PATENT WITHIN THE NTIS LICENSED PATENTS OR THE GEN-PROBE LICENSED PATENTS;

(d) THAT THE PRACTICE OF THE NTIS LICENSED PATENTS OR THE GEN-PROBE LICENSED PATENTS WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY OR PROPERTY RIGHTS OF THIRD PARTIES; OR

(e) THAT THE NTIS LICENSED PATENTS OR THE GEN-PROBE LICENSED PATENTS ARE FREE FROM INFRINGEMENT BY THIRD PARTIES.

9.2 NOTHING IN THIS AGREEMENT SHALL BE CONSTRUED AS:

(a) AN OBLIGATION TO BRING OR PROSECUTE ACTIONS OR SUITS AGAINST THIRD PARTIES FOR INFRINGEMENT;

(b) AN OBLIGATION OF GEN-PROBE TO MAINTAIN ANY PATENT OR CONTINUE TO PROSECUTE ANY PATENT APPLICATION INCLUDED WITHIN THE NTIS LICENSED PATENTS OR THE GEN-PROBE LICENSED PATENTS IN ANY COUNTRY;

(c) AN OBLIGATION OF EITHER PARTY TO FURNISH ANY CONFIDENTIAL

INFORMATION OR KNOW-HOW TO THE OTHER PARTY EXCEPT AS SPECIFIED HEREIN;

(d) CREATING ANY AGENCY, PARTNERSHIP, JOINT VENTURE OR SIMILAR RELATIONSHIP BETWEEN GEN-PROBE AND ISIS; OR

(e) CONFERRING BY IMPLICATION, ESTOPPEL OR OTHERWISE ANY LICENSE, AGREEMENT, IMMUNITY OR RIGHT UNDER ANY PATENT OF GEN-PROBE OTHER THAN THOSE SPECIFIED IN THIS AGREEMENT.

9.3 GEN-PROBE SHALL NOT BE LIABLE TO ISIS, ISIS' SUCCESSORS OR ASSIGNS OR ANY THIRD PARTY WITH RESPECT TO ANY CLAIM ARISING FROM THE USE OF THE NTIS LICENSED PATENTS OR THE GEN-PROBE LICENSED PATENTS, OR ANY CLAIM FOR LOSS OF PROFITS, LOSS OR INTERRUPTION OF BUSINESS, OR FOR INDIRECT, SPECIAL OR CONSEQUENTIAL DAMAGES OF ANY KIND.

ARTICLE X
TERM AND TERMINATION

10.1 Term. Unless sooner terminated as provided herein, this Agreement shall begin on December 19, 1997 and shall remain in effect until the last payment of the final contingent payment owed on the last to expire of the NTIS Licensed Patents and the Gen-Probe Licensed Patents, unless earlier terminated as provided in this Article X.

10.2 Termination for Cause. Except as otherwise provided in Article XII, either party may terminate the Agreement upon or after the breach of any material provision of the Agreement by the other party if the other party has not cured such breach within thirty (30) days after notice thereof by the non-breaching party, unless the breach is not curable within thirty (30) days in which case breaching party must be taking reasonable and timely steps to cure said breach. In the event that after the Closing, either party terminates this Agreement under this Article X, the provisions listed in Section 10.4 shall survive such termination and such termination shall not affect (i) the assignment and assumption of the Acquired Business pursuant to Article 11, (ii) the obligation of Isis to continue paying contingent consideration to Gen-Probe pursuant to Articles IV, V and VI, or (iii) Isis's indemnification and insurance obligations pursuant to Article XI.

10.3 Termination by the Public Health Service. In the event that the Public Health Service terminates the Amended License Agreement in accordance with Article XI of the Amended License Agreement, all rights assigned herein with respect to such Amended License Agreement and all duties assumed by either party with respect to such Amended License Agreement only and not with respect to any other obligation hereunder, shall terminate effective as of the date

of termination by the Public Health Service. Gen-Probe shall have no liability for such termination, except as specifically set forth in this Agreement, or for any action taken by any other co-exclusive licensee of the NTIS Licensed Patents.

10.4 Survival. Upon the expiration or termination of this Agreement, the following provisions of this Agreement shall survive: Articles I, II, IV, V, VI, VII, IX, X, XI, XII and XIV.

ARTICLE XI
INDEMNIFICATION AND INSURANCE

11.1 Indemnification-Isis. Isis shall indemnify and hold Gen-Probe harmless from all claims, demands, liabilities, product liability, damages and expenses, including attorneys' fees and costs arising out of any breach of the Agreement by Isis, including but not limited to, manufacturing, use or sale of the Transferred Products or any act or omission of Isis, its Affiliates or sublicenses in connection with its activities contemplated by the Agreement.

11.2 Indemnification-Gen-Probe. Gen-Probe shall indemnify and hold Isis harmless from all claims, demands, liabilities, damages and expenses, including attorneys' fees and costs arising out of any breach of the Agreement by Gen-Probe, including a breach of Gen-Probe's representation that it is transferring substantially all of the business of Gen-Probe related to NTIS Products to Isis ("Transfer Representation").

11.3 Insurance. Isis shall procure and maintain in full force and effect, at all times during the term of this Agreement, the following insurance through companies rated no less than B+ VII under Best's most recent rating guide:

Comprehensive General Liability and Product Liability insurance covering the research, development, manufacture and sales of Transferred Products by Isis with a combined single limit of Five Million Dollars for bodily injury, death and property damage. Said liability insurance policy shall name as additional insured Gen-Probe Incorporated. Said liability insurance shall recognize and insure performance by Isis of the indemnity provisions, to the extent possible, herein contained in such amount as is stated herein, which insurance shall name Gen-Probe as an additional insured. Isis shall maintain such insurance for so long as it continues to research, develop, manufacture or sell any Transferred Products, and thereafter for so long as Isis maintains insurance for itself covering such research, development, manufacture or sales.

No later than thirty (30) days after execution of this Agreement, Isis shall provide Gen-Probe with a valid certificate of insurance confirming purchase of said insurance and the inclusion of Gen-Probe Incorporated as an additional

insured. The certificate will further confirm that at least thirty (30) days prior written notice will be furnished to Gen-Probe by the insurer before any material change, cancellation, or non-renewal of the policy. It is further agreed that any coverage extended by reason of this paragraph shall be primary and that any similar insurance maintained by Gen-Probe for its own protection shall be secondary or excess and not contributing insurance.

ARTICLE XII
ARBITRATION

Any controversy, claim or dispute existing out of or relating to this Agreement, or the breach thereof, shall be resolved by binding arbitration in San Diego County, State of California and any judgment upon the award rendered by arbitration may be entered in any Court having jurisdiction. If arbitration is necessary pursuant to this paragraph, the Parties shall agree upon a single arbitrator. If the Parties are unable to agree on an arbitrator, then they will obtain nominations of three potential arbitrators from JAMS/Endispute and each party will have the right to strike one candidate's name from the list. JAMS/Endispute will then designate the arbitrator. Any arbitration award shall also include, but shall not be limited to, any and all court or arbitration costs, attorney fees and any other costs or charges reasonably necessary to adjudicate the controversy, in addition to any and all damages deemed fair by the Arbitrator(s). Nothing contained herein shall deprive any party of its right to obtain injunctive or other equitable relief.

ARTICLE XIII
FORCE MAJEURE

Neither party shall be held liable or responsible to the other party nor be deemed to have defaulted under or breached the Agreement for failure or delay in fulfilling or performing any term of the Agreement to the extent, and for so long as, such failure or delay, other than the payment of money, is caused by or results from causes beyond the reasonable control of the affected party including but not limited to fire, floods, embargoes, war, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, acts of God or acts, omissions or delays in acting by any governmental authority or other party.

ARTICLE XIV
MISCELLANEOUS

14.1 Notices. Any consent, notice or report required or permitted to be given or made under the Agreement by one of the Parties hereto to the other party shall be in writing, delivered personally or by facsimile (and promptly confirmed by personal delivery, prepaid registered or certified mail or courier), prepaid registered or certified mail or courier, addressed to such other party at its

address indicated below, or to such other address as the addressee shall have last furnished in writing to the addressor and (except as otherwise provided in the Agreement) shall be effective upon delivery to the addressee as confirmed by written proof of receipt.

If to Gen-Probe:
Gen-Probe Incorporated
10210 Genetic Center Drive
San Diego, California 92121
Attention: President
Facsimile: (619) 410-8901
cc: General Counsel

If to Isis:
Isis Pharmaceuticals, Inc.
Carlsbad Research Center
2292 Faraday Avenue
Carlsbad, California 92008
Attention: President
Facsimile: (619) 931-9639
cc: General Counsel

14.2 Governing Law. This Agreement shall be governed by and construed in accordance with the laws of the State of California without regard to its conflicts of law principles. The Parties hereby consent to the venue and jurisdiction of such laws and courts.

14.3 Assignment. This Agreement may not be assigned by either party without the prior written consent of the other party, except that either party may assign this Agreement to any of its Affiliates or to a successor in connection with the merger, consolidation, or sale of all or substantially all of its assets or that portion of its business pertaining to the subject matter of this Agreement, with prompt written notice to the other party of any such assignment.

14.4 Irreparable Harm. The Parties agree that irreparable damage will occur in the event that the provisions of Articles II, III and VII are not specifically enforced. In the event of a breach or threatened breach of any such provisions, the parties agree that the non-breaching party shall, in addition to all other remedies, be entitled to temporary or permanent injunction, without showing any actual damage or that monetary damages would not provide an adequate remedy and without the necessity of posting any bond, and/or a decree for specific performance, in accordance with the provisions hereof.

14.5 Waivers and Amendments. No change, modification, extension, termination or waiver of this Agreement, or any of the provisions, shall be valid unless made in writing and signed by authorized representatives of both Parties.

14.6 Attorneys' Fees. If either party hereto commences an arbitration or other action against the other party to enforce any of the terms hereof or because of the breach by such other party of any of the terms hereof, the prevailing party shall be entitled, in addition to any other relief granted, to all actual out-of-pocket costs and expenses incurred by such prevailing party in connection with such action, including, without limitation, all reasonable attorneys' fees, and a right to such costs and expenses shall be deemed to have accrued upon the commencement of such action and shall be enforceable whether or not such acting is prosecuted to judgment.

14.7 Entire Agreement. This Agreement embodies the entire understanding between the Parties and supersedes any prior understanding and agreements between them respecting the subject matter hereof. There are no representations, agreements, arrangements or understandings, oral or written, between the Parties relating to the subject matter of this Agreement which are not fully expressed herein.

14.8 Severability. Any of the provisions of this Agreement which are determined to be invalid or unenforceable in any jurisdiction shall be ineffective to the extent of such invalidity or unenforceability in such jurisdiction, without rendering invalid or unenforceable the remaining provisions hereof and without affecting the validity or enforceability of any of the terms of this Agreement

in any other jurisdiction.

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

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

IN WITNESS WHEREOF, the Parties have hereunto have affixed their authorized signatures.

GEN-PROBE INCORPORATED	ISIS PHARMACEUTICALS, INC.
By: H.L. NORDHOFF	By: B. LYNNE PARSHALL
Name: H.L. Nordhoff	Name: B. Lynne Parshall
Title: CEO	Title: EXECUTIVE VICE PRESIDENT

16

SCHEDULE A

"ACQUIRED ASSETS"

* The NTIS Agreements and all rights thereunder in and to the NTIS Licensed Patents;

* Any sublicenses granted with respect to the NTIS Agreements, any rights thereunder, remedies against infringements thereof, and rights to protection of interests therein under the laws of all jurisdictions;

* All records, ledgers, files, documents, correspondence, lists, drawings, and specifications, studies, reports, and other printed or written materials related to the NTIS Agreements in Gen-Probe's possession which postdate the Amended License Agreement between Gen-Probe and the Public Health Service;

* Tangible personal property (including machinery, equipment, inventories of raw materials and supplies, manufactured and purchased parts), if any, used by Gen-Probe exclusively to research, develop and produce the Transferred Products;

* Accounts, notes, and other receivables, if any, owed to Gen-Probe solely in connection with the research, development and production of the Transferred Products; and

* Any good will associated with Gen-Probe's business related to the Transferred Products.

17

EXHIBIT A

[*CONFIDENTIAL TREATMENT REQUESTED FOR

ENTIRE CONTENTS OF EXHIBIT A]

18

EXHIBIT B

[*CONFIDENTIAL TREATMENT REQUESTED FOR

ENTIRE CONTENTS OF EXHIBIT B]

19

EXHIBIT C

[*CONFIDENTIAL TREATMENT REQUESTED FOR

ENTIRE CONTENTS OF EXHIBIT C]

20

EXHIBIT D

GEN-PROBE LICENSED PATENTS

21

EXHIBIT D

1. OLIGONUCLEOTIDES WITH ACTIVITY AGAINST HUMAN IMMUNODEFICIENCY VIRUS
(U.S. Application Serial No. 08/094,390, filed 7/19/93 - abandoned)
Continuation-In-Part Application filed 7/19/94, Serial No. 08/279,751 -
Issued 5/13/97 as Patent No. 5,629,413 - expires 5/13/2014

2. (*)

3. COMPOUNDS AND METHODS OF INHIBITING PROPAGATION OF HUMAN IMMUNNODEFICIENCY VIRUS
(U.S. Application Serial No. 08/277,857, filed 7/19/94 - Allowed -
Awaiting Issuance)

4. (*)

5. ENZYMATIC SYNTHESIS OF OLIGONUCLEOTIDES; USING DIGESTIBLE TEMPLATES
(U.S. Application Serial No. 08/484,519, filed 6/7/95 - pending)

6. ENZYMATIC SYNTHESIS OF A PLURALITY OF OLIGONUCLEOTIDES FROM A SINGLE TEMPLATE
(U.S. Application Serial No. 08/484,668, filed 6/7/95, abandoned
and File-Wrapped as 08/850,951, filed 5/5/97 - pending)

7. THE USE OF RESTRICTION ENDONUCLEASE SEQUENCES USEFUL FOR CLEAVING PHOSPHOROTHIOATE OLIGONUCLEOTIDES
(U.S. Application Serial No. 08/484,816, filed 6/7/95 - Issued 7/29/97 as
Patent No. 5,652,126 - expires 6/7/2015)

8. ENZYMATIC SYNTHESIS OF PHOSPHOROTHIOATE OLIGONUCLEOTIDES USING RESTRICTION ENDONUCLEASES
(U.S. Application Serial No. 08/476,625, filed 6/7/95 - Allowed -
Awaiting Issuance)

9. ENZYMATIC SYNTHESIS OF OLIGONUCLEOTIDES USING 3'-RIBONUCLEOTIDE PRIMERS
(U.S. Application Serial No. 08/477,228, filed 6/7/95, abandoned and
File-Wrapped on 10/10/97 - Serial No. to be assigned - pending)

   a.) TEMPLATE AND PRIMER BASED SYNTHESIS OF ENZYMATICALLY CLEAVABLE OLIGONUCLEOTIDES
   (Consolidated European Application - Nos. 5, 6, 7, 8 & 9) - EPO
   Publication No. EPO 747 479 - published 12/11/96

10. OLIGONUCLEOTIDES SPECIFIC FOR CYTOKINE SIGNAL TRANSDUCER GP130 MRNA
(U.S. Application Serial No. 08/476,634, filed 6/7/95 - Issued 10/7/97 as
Patent No. 5,674,995 - expires 6/7/2015)
10/3/97 a Continuation Application was filed claiming priority to
08/476,634, Serial No. to be assigned

EXHIBIT D (CONT.)

11. METHOD FOR INHIBITING CELLULAR PROLIFERATION USING ANTISENSE OLIGONUCLEOTIDES TO GP13O MRNA
(U.S. Application Serial No.08/484,518, filed 6/7/95 - allowed - awaiting issuance)

a. OLIGONUCLEOTIDES SPECIFIC For CYTOKINE SIGNAL TRANSDUCER GP13O MRNA
(Consolidated European Application - Nos. 10 & 11)
EPO Publication No. EPO 747 480, published 12/11/96

12. OLIGONUCLEOTIDES SPECIFIC FOR INTERLEUKIN 6 RECEPTOR MRNA AS INHIBITORS OF DISEASE - ASSOCIATED CELLULAR PROLIFERATION
(U.S. Application Serial No. 08/484,666, filed 6/7/95 - Abandoned)

13. METHOD FOR INHIBITING CELLULAR PROLIFERATION USING ANTISENSE OLIGONUCLEOTIDES TO INTERLEUKIN-6 RECEPTOR MRNA
(U.S. Application Serial No. 08/486,408, filed 6/7/95 - Allowed - Awaiting Issuance) - Considering filing a Continuation Application before issuance

a. METHOD AND ANTISENSE OLIGONUCLEOTIDES TO INTERLEUKIN-6 RECEPTOR MRNA FOR INHIBITING CELLULAR PROLIFERATION
(Consolidated European Application - Nos. 12 & 13)
EPO Publication No. EPO 747 386, published 12/11/96

EXHIBIT E

NTIS LICENSED PATENTS

EXHIBIT E

United States

U.S. Patent Application 07/030,073 (now abandoned), filed on March 25, 1987 and entitled "Phosphorothioated Analogues of Oligodeoxyribonucleotides as Inhibitors for the Replication and Cytopathic Effects of HTLV-III"

U.S. Patent 5,276,019 (filed on October 17, 1988 as U.S. Patent Application 07/159,017, which is a continuation-in-part of U.S. Patent Application 07/030,073), issued on January 4, 1994 and entitled "Inhibitors for Replication of Retroviruses and for the Expression of Oncogene Products"

U.S. Patent 5,268,717 (filed on November 16, 1992 as U.S. Patent Application 07/976,777, which is a divisional of U.S. Patent Application 07/159,017), issued on February 15, 1994 and entitled "Inhibitors for Replication of Retroviruses and for the Expression of Oncogene Products"

U.S. Patent 5,264,423 (filed on November 16, 1992 as U.S. Patent Application 07/976,733, which was a continuation of U.S. Patent Application 07/159,017), issued on November 23, 1993 and entitled "Inhibitors for Replication of Retroviruses and for the Expression of Oncogene Products"

Foreign

PCT/US88/01024 filed on March 24, 1988

Australia - 15717/88

Canada - 562318

EPO - 88302617.1

Israel - 85827

Japan - Sho 63-503266

EXHIBIT 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT AUDITORS

We consent to the incorporation by reference in the Registration Statements (Form S-3 No. 33-72124, 33-75068 and 33-96138 and Form S-8 No. 33- 51236, 33-42970, 33-42356, 33-54840, 33-58450, 33-43330, 33-75150, 33-90780 and 333-05825) of Isis Pharmaceuticals, Inc. of our report dated January 23, 1998, with respect to the financial statements of Isis Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 1997.

ERNST & YOUNG LLP

San Diego, California
March 13, 1998

<ARTICLE> 5
<LEGEND>
This schedule contains summary financial information derived from the Company's audited Balance Sheet as of December 31, 1997 and audited Statements of Operations for the Twelve Months Ended December 31, 1997 and is qualified in its entirety by reference to such financial statements.
</LEGEND>
<MULTIPLIER> 1,000

<PERIOD-TYPE>	12-MOS	
<FISCAL-YEAR-END>		DEC-31-1996
<PERIOD-START>		JAN-01-1997
<PERIOD-END>		DEC-31-1997
<CASH>		38,102
<SECURITIES>		48,684
<RECEIVABLES>		0
<ALLOWANCES>		0
<INVENTORY>		0
<CURRENT-ASSETS>		89,150
<PP&E>		18,785
<DEPRECIATION>		0
<TOTAL-ASSETS>		117,881
<CURRENT-LIABILITIES>		26,577
<BONDS>		56,452
<PREFERRED-MANDATORY>		0
<PREFERRED>		0
<COMMON>		27
<OTHER-SE>		34,825
<TOTAL-LIABILITY-AND-EQUITY>		117,881
<SALES>		0
<TOTAL-REVENUES>		36,537
<CGS>		0
<TOTAL-COSTS>		0
<OTHER-EXPENSES>		64,018
<LOSS-PROVISION>		0
<INTEREST-EXPENSE>		3,585
<INCOME-PRETAX>		(31,066)
<INCOME-TAX>		0
<INCOME-CONTINUING>		(31,066)
<DISCONTINUED>		0
<EXTRAORDINARY>		0
<CHANGES>		0
<NET-INCOME>		(31,066)
<EPS-PRIMARY>		(1.17)
<EPS-DILUTED>		(1.17)