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SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended June 30, 2001
OR

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

For the transition period from _____ to _____

Commission file number 0-19125

ISIS PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporations or organization)	(I.R.S. Employer Identification No.)

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

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

(1) Yes X No (2) Yes X No

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

Common stock $.001 par value	**42,247,956 shares**
(Class)	(Outstanding at June 30, 2001)

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ISIS PHARMACEUTICALS, INC.

CONDENSED BALANCE SHEETS

(in thousands, except share data)

	June 30, 2001	December 31, 2000
	(Unaudited)	(Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 12,736	$ 39,615
Short-term investments	93,562	87,647
Contracts receivable	2,098	3,346
Prepaids and other current assets	2,545	2,596
Total current assets	110,941	133,204
Property, plant and equipment, net	23,330	22,625
Licenses, net	29,934	500
Patents, net	15,016	13,815
Investments in affiliates	7,094	12,491
Deposits and other assets	1,213	621
Total assets	$ 187,528	$ 183,256
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,805	$ 2,231
Accrued compensation	2,744	3,598
Accrued liabilities	1,742	1,429
Deferred revenues	5,877	2,771
Current portion of long term obligations	12,766	4,607
Total current liabilities	25,934	14,636
Long-term obligations, less current portion	115,666	102,254
Stockholders' equity:		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value, 120,150 shares authorized, issued and outstanding at June 30, 2001 and December 31, 2000	12,015	12,015
Accretion of Series A Preferred stock dividends	1,376	1,050
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value, 16,620 shares authorized,	12,015	12,015

12,015 shares issued and outstanding at June 30, 2001 and December 31, 2000		
Accretion of Series B Preferred Stock dividends	899	584
Common stock, $.001 par value, 100,000,000 shares authorized, 42,247,956 shares and 40,085,447 shares issued and outstanding at June 30, 2001 and December 31, 2000, respectively	42	40
Additional paid-in capital	377,333	352,854
Deferred compensation	(329)	(858)
Accumulated other comprehensive income	569	126
Accumulated deficit	(357,992)	(311,460)
Total stockholders' equity	45,928	66,366
Total liabilities and stockholders' equity	$ 187,528	$ 183,256

Note: The balance sheet at December 31, 2000 has been derived from the audited financial statements at that date.
See accompanying notes.

ISIS PHARMACEUTICALS, INC.

CONDENSED STATEMENTS OF OPERATIONS

(in thousands, except for per share amounts)

(Unaudited)

	Three months ended June 30,		Six months ended June 30,	
	2001	2000	2001	2000
Revenue:				
Research and development revenues under collaborative agreements	$ 5,114	$ 4,139	$ 7,903	$ 6,888
Research and development revenues from affiliates	2,432	2,761	4,148	3,929
Licensing and royalty revenue	46	85	174	222
Total revenue	7,592	6,985	12,225	11,039
Expenses:				
Research and development	19,924	12,746	39,059	25,985
General and administrative	2,778	2,414	5,593	4,238
Compensation related to stock options	1,354	—	1,271	—
Restructuring activities	—	—	—	1,608
Total operating expenses	24,056	15,160	45,923	31,831
Loss from operations	(16,464)	(8,175)	(33,698)	(20,792)
Equity in loss of affiliates	(4,194)	(4,594)	(8,158)	(8,089)
Interest income	1,106	1,596	3,083	2,488
Interest expense	(3,491)	(3,129)	(7,117)	(6,236)
Net loss	(23,043)	(14,302)	(45,890)	(32,629)
Accretion of dividends on preferred stock	(323)	(306)	(642)	(587)
Net loss applicable to common stock	$ (23,366)	$ (14,608)	$ (46,532)	$ (33,216)
Basic and diluted net loss per share	$ (0.58)	$ (0.40)	$ (1.15)	$ (0.95)
Shares used in computing basic and diluted Net loss per share	40,492	36,979	40,322	35,021

See accompanying notes.

CONDENSED STATEMENTS OF CASH FLOWS

(In thousands)

(Unaudited)

	Six months ended June 30,	
	2001	**2000**
Net cash used in operating activities	$ (24,222)	$ (19,385)
Investing activities:		
Short-term investments	(5,472)	(40,745)
Property and equipment	(3,006)	(924)
Licenses and other assets	(17,683)	(876)
Investment in affiliates	(3,333)	(15,865)
Net cash used in investing activities	(29,494)	(58,410)
Financing activities:		
Net proceeds from issuance of equity securities	24,379	102,103
Proceeds from long-term borrowings	4,043	3,850
Principal payments on debt and capital lease obligations	(1,585)	(1,411)
Net cash provided from financing activities	26,837	104,542
Net (decrease) increase in cash and cash equivalents	(26,879)	26,747
Cash and cash equivalents at beginning of period	39,615	35,296
Cash and cash equivalents at end of period	$ 12,736	$ 62,043
Supplemental disclosures of cash flow information:		
Interest paid	$ 1,524	$ 530
Supplemental disclosures of non-cash investing and financing activities:		
Conversion of preferred stock dividends into preferred stock	$ —	$ 308
Additions to debt for licensing costs	$ 13,500	$

See accompanying notes.

ISIS PHARMACEUTICALS, INC.

NOTES TO FINANCIAL STATEMENTS

(Unaudited)

1. Basis of Presentation

The unaudited interim financial statements for the six month periods ended June 30, 2001 and 2000 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 2000. The financial statements include all adjustments (consisting only of normal recurring adjustments) which the Company considers necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2000 included in the Company's Annual Report on Form 10-K/A filed with the Securities and Exchange Commission.

Revenue Recognition

Revenue is generally recognized when all contractual obligations have been satisfied and collection of the resulting receivable is reasonably assured. Research and development contract revenues from cost-reimbursement agreements are recorded as the related expenses are incurred, up to the contractual limits. Payments received that are related to future performance are deferred and recorded as revenue as they are earned over specified future performance periods. Research and development payments for which no services are required to be performed in the future are recognized as revenues upon receipt of such payments. Revenues related to nonrefundable, upfront fees are recognized over the period of the contractual arrangements as performance obligations related to the services to be provided have been satisfied. Revenue from product sales is recognized at the time products are shipped.

Use of Estimates

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

2. Strategic Alliances

Affiliates

Isis currently has two joint ventures with Elan Corporation, plc (Elan). In April 1999, Orasense Ltd. (Orasense) was formed to develop technology for the formulation of oral oligonucleotide drugs. In January 2000, the second joint venture, HepaSense Ltd. (HepaSense), was formed to treat patients chronically infected with the Hepatitis C virus. Both affiliates are Bermuda limited companies. Each entity's outstanding common stock is owned 80.1% by Isis and 19.9% by Elan.

Elan and its subsidiaries have retained significant minority investor rights that are considered "participating rights" as defined in EITF 96-16 in each entity. Therefore, Isis does not consolidate the financial statements of Orasense or HepaSense, but instead accounts for the investments in each under the equity method of accounting. For the quarter and six month periods ended June 30, 2001, Isis recognized $2.4 million and $4.1 million, respectively, in revenue for research and development activities performed for these joint ventures. For the three and six month periods ended June 30, 2000,

Isis reported $2.8 million and $3.9 million in revenue, respectively. These amounts are included as research and development revenues from affiliates for the respective periods.

The results of operations of Orasense for the quarter and six month periods ended June 30, 2001 and 2000 are as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2001	2000	2001	2000
Revenue	$ —	$ —	$ —	$ —
Research and development expense	3,173	3,037	5,633	6,151
Net loss	$ (3,173)	$ (3,037)	$ (5,663)	$ (6,151)

The results of operations of HepaSense for the quarter and six month periods ended June 30, 2001 and 2000 are as follows (in thousands):

	Three Months Ended June 30,		Six Months Ended June 30,	
	2001	2000	2001	2000
Revenue	$ —	$ —	$ —	$ —
Research and development expense	2,062	2,689	4,216	3,939
Net loss	$ (2,062)	$ (2,689)	$ (4,216)	$ (3,939)

Agouron Pharmaceuticals, Inc., a Pfizer Company

In May 2001, Ibis Therapeutics™, a division of Isis, earned a $2.5 million research milestone payment from Agouron Pharmaceuticals, Inc., a Pfizer Company (Pfizer), for progress in Ibis' collaboration to discover small molecule drugs that bind to RNA. The payment was included as research and development revenue under collaborative agreements for the three and six month periods ended June 30, 2001.

Merck & Company, Inc.

In May 2001, Isis and Merck & Company, Inc. (Merck) announced that Isis licensed its preclinical Type 2 diabetes antisense drug candidate, ISIS 113715, to Merck. Merck will undertake the future development and commercialization of the compound. Isis received an upfront payment for certain expenses associated with the preclinical development of the drug. In addition, Merck will make a series of milestone payments to Isis on the achievement of development and regulatory milestones for the drug. Merck will also make royalty payments based on sales of the drug. Isis recorded a portion of the payment as research and development revenue during the second quarter of 2001 with the balance to be recognized over the period of Isis' continued involvement with the agreement.

Hybridon, Inc.

In May 2001, Isis and Hybridon, Inc. entered into an agreement under which Isis acquired an exclusive license to all of Hybridon's antisense chemistry and delivery patents and technology. Hybridon received a license to Isis' suite of RNase H patents. In exchange for the license to Hybridon's antisense patents, Isis paid $15.0 million in cash and will pay Hybridon $19.5 million in Isis common stock over the next two years. In return for access to Isis' patents, Hybridon will pay Isis $6.0 million in Hybridon common stock over the next three years. Isis' balance sheet at June 30, 2001 reflects a licensing asset for the net amount of $28.3 million related to this agreement.

3. Comprehensive Loss

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

Statements of Comprehensive Loss (Unaudited)

	Three Months Ended June 30,		Six Months Ended June 30,	
	2001	2000	2001	2000
Comprehensive loss:				
Change in unrealized gains(losses)	$ (30)	$ (68)	$ 443	$ 3
Net loss	(23,366)	(14,608)	(46,532)	(33,216)
Comprehensive loss	$ (23,396)	$ (14,676)	$ (46,089)	$ (33,213)

4. Financing

In June 2001, Isis issued 1,986,874 shares of common stock at prices ranging from $11.03 to $11.50 per share.

5. Subsequent Events

In July 2001, Isis entered into a collaboration with PE Corporation through the Celera Genomics Group (Celera), in which Celera will employ Isis' GeneTrove division to identify the biological role of more than 200 genes. Isis will recognize the related revenue over the 18 month term of the agreement as the services are performed.

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

This Form 10-Q contains forward-looking statements regarding our business and the therapeutic and commercial potential of our technologies and products in development. Such statements are subject to certain risks and uncertainties, particularly those risks and uncertainties inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, and the endeavor of building a business around such potential products. Actual results could differ materially from those discussed in this Form 10-Q. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in our Annual Report on Form 10-K/A for the year ended December 31, 2000 which is on file with the U.S. Securities and Exchange Commission and those identified in the section of Item 2 entitled "Risk Factors" of this report. As a result, the reader is cautioned not to rely on these forward-looking statements.

Since our inception in January 1989, almost all of our resources have been devoted to research, drug discovery and drug development programs. We are not yet profitable and expect to continue to have operating losses for the next several years. Our revenue comes from collaborative research and development agreements with pharmaceutical companies, the sale and licensing of our intellectual property, research grants and interest income. The revenue from the collaboration agreements increases the amount of research and development activity that we are able to fund and offsets a portion of our research and development costs. In 1998, we received approval from the U.S. Food and Drug Administration, or FDA, to begin marketing our first product, Vitravene™, a drug used to treat CMV retinitis.

Results of Operations

Our total revenue for the quarter and six months ended June 30, 2001 was $7.6 million and $12.2 million, respectively, compared to $7.0 million and $11.0 million for the same periods of 2000. The increase in revenue for the quarter and six months ended June 30, 2001 compared to the same periods of 2000, was due primarily to our licensing of ISIS 113715, a preclinical Type 2 diabetes candidate, to Merck and the $2.5 million milestone that our Ibis Therapeutics division earned in its collaboration with Pfizer. The increase was partially offset by the conclusion of research funding from AstraZeneca and certain government grants.

Our research and development expenses were $19.9 million for the three months ended June 30, 2001, and $39.1 million for the six months ended June 30, 2001, compared with $12.7 million and $26.0 million for the same periods of 2000. The increase in expenses in 2001 compared to 2000 was driven by the cost of preclinical and clinical activities to advance the development of our drugs. Currently we have eleven products in development, up from seven in the same period of last year. Additionally, seven of the eleven products are in the more expensive stages of development, Phase 2 or Phase 3 clinical trials.

Our general and administrative expenses increased slightly to $2.8 million for the second quarter and $5.6 million for the six months ended June 30, 2001, from $2.4 million and $4.2 million for the same periods of 2000. The increase was primarily due to additional expense required to support our increasing research and development activities.

Our compensation related to stock options for the quarter and six months ended June 30, 2001 was $1.4 million and $1.3 million, respectively. There was no similar expense recorded for the same periods of 2000. The expense was primarily a result of an exchange we made regarding certain existing options to non-officer employees completed in January 2000. These exchanged options are required to be accounted for as variable stock options in accordance with Financial Accounting Standards Board Interpretation No. 44. Variable stock options can result in significant increases and decreases in compensation expense subject to the variability of our stock price. In addition, we account for stock

options granted to consultants in accordance with EITF 96-18, which also contributed to these expenses.

Our interest expense for the quarter and six months ended June 30, 2001 was $3.5 million and $7.1 million, respectively, compared to $3.1 million and $6.2 million for the same periods of 2000. The increase was due to the increase in debt on the convertible debt facilities available to us from Elan to fund research and development activities for Orasense and HepaSense. During the second quarter we borrowed an additional $3.3 million resulting in a June 30, 2001 balance of $15.6 million, compared to $6.4 million for the same period of 2000. Also contributing to the increase in our interest expense, was the interest accruing on our

$40 million debt financing that was completed in the fourth quarter of 1997 and the second quarter of 1998. In this financing, interest accrues for the first five years and no principal payments are due for 10 years.

Interest income decreased to $1.1 million for the second quarter and increased to $3.1 million for the six months ended June 30, 2001, from $1.6 million and $2.5 million for the same periods of 2000. The decrease in interest income for the quarter ended June 30, 2001 compared to the same period of 2000 is related to lower average cash and investment balances for the quarter combined with lower rates of return on investments in 2001 compared to 2000. The increase in interest income for the six months ending June 30, 2001 compared to the same period in 2000 was due to higher average investment balances during the 2001 period offset by lower rates of return in 2001 compared to 2000.

During the quarter and six months ended June 30, 2001 we recorded a net loss applicable to common stock of $23.4 million and $46.5 million, or $0.58 and $1.15 per share, respectively, compared with $14.6 million and $33.2 million, or $0.40 and $0.95 per share, respectively, for the same periods in 2000. Our loss from operations was $16.5 million for the second quarter of 2001, compared to $8.2 million for the same period in 2000. The increases in our net loss applicable to common stock and loss from operations were primarily the result of increased operating expenses related to the eleven products we have in development, including the ongoing Phase 3 trial of Isis 3521 in patients with non small cell lung cancer. This program, the planned Phase 3 trial of Isis 2302 in patients with Crohn's disease, and the continued aggressive development of the remaining drugs in our pipeline, will result in increased expenses and lead to an increase in our net loss from operations for 2001 over our 2000 net loss from operations. Additionally, non-cash compensation related to stock options included in expenses for the quarter and six months ended June 30, 2001 was $1.4 million and $1.3 million, respectively. We expect operating losses to fluctuate from quarter to quarter because of differences in the timing of revenue recognized, and expenses incurred.

We believe that inflation and changing prices have not had a material effect on our operations to date.

Liquidity and Capital Resources

We have financed our operations with revenue from contract research and development, revenue from the sale or licensing of our intellectual property, the sale of our equity securities, and the issuance of long-term debt. From our inception through June 30, 2001, we have earned approximately $230 million in revenue from contract research and development and the sale and licensing of our intellectual property. Since we were founded, we have raised net proceeds of approximately $392 million from the sale of equity securities. We have borrowed approximately $86.3 million under long-term debt arrangements to finance a portion of our operations.

As of June 30, 2001, we had cash, cash equivalents and short-term investments totaling $106.3 million and working capital of $85.0 million. In comparison, we had cash, cash equivalents and short-term investments of $127.3 million and working capital of $118.6 million as of December 31, 2000. The decreases in our cash, cash equivalents and short-term investments, and working capital in 2001 from 2000 were due primarily to cash used to fund our operations, and the decision to strengthen

our intellectual property by entering into a licensing agreement with Hybridon, Inc. The decrease was partially offset by the sale of our common stock to an institutional investor in the second quarter of 2001.

In 1997 and 1998, we borrowed a total of $40 million in private transactions. The loans bear interest at 14% per annum and must be repaid on November 1, 2007. The interest accrues during the first five years of the loans. After the first five years, interest must be paid quarterly. No principal payments are required until November 1, 2007. In conjunction with these transactions, we issued warrants to purchase 800,000 shares of common stock at a price of $25 per share. The warrants issued in connection with both of these financings expire on November 1, 2004. Because interest is accrued during the first five years, the balance of these borrowings will accrue to a total of $78 million on November 1, 2002. The debt under these arrangements is carried on our balance sheet, net of the amortized amount allocated to the warrants and including accrued interest. The combined carrying amount of these notes at June 30, 2001 was $64.8 million.

As of June 30, 2001, our long-term obligations totaled $115.7 million, versus $102.3 million at December 31, 2000. The increase was primarily due to the accrual of interest on the ten-year notes described above and our convertible debt facilities. This increase was partially offset by principal repayments on existing obligations. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our growing business. We will continue to use lease financing as long as the terms remain commercially attractive. We believe that our existing cash, cash equivalents and short-term investments at June 30, 2001, combined with contract revenue and interest income should be sufficient to fund our operations for the next 30 to 36 months.

RISK FACTORS

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

Our business will suffer if we fail to obtain regulatory approval for our products.

We must conduct time-consuming, extensive and costly clinical trials, in compliance with U.S. Food and Drug Administration regulations, and by comparable authorities in other countries, to show the safety and efficacy of each of our drug candidates, as well as the optimum dosage for each, before the FDA can approve a drug candidate for sale. We may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our products under development. Delays in receiving these approvals, failure by us or our partners to receive these approvals at all or failure to comply with existing or future regulatory requirements could have a material adverse effect on our business, financial condition and results of operations.

Significant additional trials may be required, and we may not be able to demonstrate that our drug candidates are safe or effective. We have only introduced one commercial product, Vitravene. We cannot guarantee that any of our other product candidates will obtain required government approvals or that we can successfully commercialize any products.

Our business will suffer if our products are not used by doctors to treat patients.

We cannot guarantee that any of our products in development, if approved for marketing, will be used by doctors to treat patients. We currently have one product, Vitravene, a treatment for CMV retinitis in AIDS patients, which addresses a small commercial market with significant competition. However, we may not be successful in commercializing additional products.

The degree of market acceptance for any of our products depends upon a number of factors, including: the receipt and scope of regulatory approvals; the establishment and demonstration in the medical and patient community of the clinical efficacy and safety of our product candidates and their potential advantages over competitive products; and reimbursement policies of government and third-party payors. In addition, physicians, patients, patient advocates, payors or the medical community in general may not accept and use any products that we may develop.

Our business will suffer if any of our collaborative partners fail to develop, fund or sell any of our products under development or if we are unable to obtain additional partners.

If any collaborative partner fails to 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 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.

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 business could suffer if the results of clinical testing indicate that any of our products under development are not suitable for commercial use.

Drug discovery and development involves inherent risks, including the risk that molecular targets prove unsuccessful and the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings or have undesirable side effects. Most of our resources are dedicated to applying molecular biology and medicinal chemistry to the discovery and development of drug candidates based upon antisense technology, a novel drug discovery tool for designing drugs that work at the genetic level to block the production of disease-causing proteins.

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

Because of the nature of the business of drug discovery and development, our expenses have exceeded our revenues since we were founded in January 1989. As of June 30, 2001, our accumulated losses were approximately $358 million. Most of the losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our growth and operations. These costs have exceeded our revenues, most of which have come from collaborative arrangements, interest income and research grants. Our product revenues to date have been derived solely from sales of Vitravene. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and we expect losses to increase as our preclinical testing and clinical trial efforts continue to expand. We cannot guarantee that we will successfully develop, receive regulatory approval for, commercialize, manufacture, market or sell any additional products, or achieve or sustain future profitability.

Our business will suffer if we fail to obtain timely funding.

Based on our current operating plan, we believe that our available cash and existing sources of revenue and credit, together with the interest earned on those funds, will be adequate to satisfy our capital needs for the next 30 to 36 months. We expect that we will need substantial additional funding in the future. Our future capital requirements will depend on many factors, such as the following: continued scientific progress in our research, drug discovery and development programs; the size of these programs and progress with preclinical and clinical trials; the time and costs involved in obtaining regulatory approvals; the costs involved in filing, prosecuting and enforcing patent claims; competing technological and market developments, including the introduction of new therapies that address our markets; costs of commercialization of products; and changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

Additional funds will need to be raised through public or private financing. Additional financing may not be available, or, if available, may not be available 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, we may be required to cut back on one or more of our research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others if available. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

Our business will suffer if we cannot manufacture our products or have a third party manufacture our products at low costs so as to enable us to charge competitive prices to buyers.

To 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.

Our business will suffer if we fail to compete effectively with our competitors.

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 other new therapeutic drug candidates that are more effective than any drug candidates that we are developing. These competitive developments could make our technology and products obsolete or non-competitive before we have had enough time to develop and commercialize our products, or 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. We will also compete with respect to manufacturing efficiency and marketing capabilities, areas in which we have limited or no experience.

Our business will suffer if we are unable to protect our patents or our proprietary rights.

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

Intellectual property litigation could harm our business

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

If a third party claimed an intellectual property right to technology we use, we might be forced to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to such intellectual property on favorable terms, if at all.

The loss of key personnel, or the inability to attract and retain highly skilled personnel, could adversely affect our business.

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our management. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific

personnel on acceptable terms, because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions.

Our stock price may continue to be highly volatile.

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. During the past twelve months, the market price of our common stock has ranged from $7.94 to $15.00 per share. The market price can be affected by many factors, including, for example, fluctuations in our operating results, announcements of clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least $66^{2}/_{3}$% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

Our certificate of incorporation also requires that any action required or permitted to be taken by our stockholders must be taken at a duly called annual or special meeting of stockholders and may not be taken by written consent. In addition, special meetings of our stockholders may be called only by the board of directors, the chairman of the board or the president, or by any holder of 10% or more of our outstanding common stock. These provisions, as well as Delaware law and other of our agreements including our stockholders' Rights Plan, may discourage certain types of transactions in which our stockholders might otherwise receive a premium for their shares over then current market prices, and may limit the ability of our stockholders to approve transactions that they think may be in their best interests. In addition, our board of directors has the authority to fix the rights and preferences of and issue shares of preferred stock, which may have the effect of delaying or preventing a change in control of Isis without action by the stockholders.

Quantitative and Qualitative Disclosures About Market Risk

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

PART II—OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

On July 9, 2001, Isis filed suit against Sequitur, Inc. in the United States District Court for the Southern District of California. The suit alleges infringement of United States Patent No. 6,001,653 entitled "Human Type 2 RNase H", which was issued to Isis on December 14, 1999.

ITEM 2. CHANGES IN SECURITIES

Not applicable.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

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

Not applicable.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a.

Exhibits

3.1	Bylaws of Isis Pharmaceuticals, Inc.
3.2	Amended and Restated Certificate of Incorporation filed April 9, 2001
10.1	Agreement between the Registrant and Merck & Co., Inc., dated May 22, 2001 (with certain confidential information deleted)
10.2	Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001 (with certain confidential information deleted)
10.3	Agreement between the Registrant and PE Corporation through the Celera Genomics Group, dated July 9, 2001 (with certain confidential information deleted)

b.

Reports on Form 8-K

Not applicable.

ISIS PHARMACEUTICALS, INC.
SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.
(Registrant)

Date: August 10, 2001 By: /s/ STANLEY T. CROOKE

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

Date: August 10, 2001 By: /s/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President and Chief Financial Officer
(Principal Financial Officer)

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BYLAWS

OF

ISIS PHARMACEUTICALS, INC.
(A DELAWARE CORPORATION)

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BYLAWS

OF

ISIS PHARMACEUTICALS, INC.
(A DELAWARE CORPORATION)

ARTICLE I

OFFICES

SECTION 1. REGISTERED OFFICE. The registered office of the corporation in the State of Delaware shall be in the City of Dover, County of Kent. (Del. Code Ann., tit. 8, Section 131)

SECTION 2. OTHER OFFICES. The corporation shall also have and maintain an office or principal place of business at such place as may be fixed by the Board of Directors, and may also have offices at such other places, both within and without the State of Delaware as the Board of Directors may from time to time determine or the business of the corporation may require. (Del. Code Ann., tit. 8, Section 122(8))

ARTICLE II

CORPORATE SEAL

SECTION 3. CORPORATE SEAL. The Board of Directors may adopt a corporate seal. The corporate seal shall consist of a die bearing the name of the corporation and the inscription, "Corporate Seal-Delaware." Said seal may be used by causing it or a facsimile thereof to be impressed or affixed or reproduced or otherwise. (Del. Code Ann., tit. 8, Section 122(3))

ARTICLE III

STOCKHOLDERS' MEETINGS

SECTION 4. PLACE OF MEETINGS. Meetings of the stockholders of the

corporation may be held at such place, either within or without the State of Delaware, as may be determined from time to time by the Board of Directors. The Board of Directors may, in its sole discretion, determine that the meeting shall not be held at any place, but may instead be held solely by means of remote communication as provided under the Delaware General Corporation Law ("DGCL"). (Del. Code Ann., tit. 8, Section 211(a))

SECTION 5. ANNUAL MEETINGS.

(a) The annual meeting of the stockholders of the corporation, for the purpose of election of directors and for such other business as may lawfully come before it, shall be held on such date and at such time as may be designated from time to time by the Board of Directors.

Nominations of persons for election to the Board of Directors of the corporation and the proposal of business to be considered by the stockholders may be made at an annual meeting of stockholders: (i) pursuant to the corporation's notice of meeting of stockholders; (ii) by or at the direction of the Board of Directors; or (iii) by any stockholder of the corporation who was a stockholder of record at the time of giving of notice provided for in the following paragraph, who is entitled to vote at the meeting and who complied with the notice procedures set forth in Section 5. (Del. Code Ann., tit. 8, Section 211(b)).

(b) At an annual meeting of the stockholders, only such business shall be conducted as shall have been properly brought before the meeting. For nominations or other business to be properly brought before an annual meeting by a stockholder pursuant to clause (c) of Section 5(a) of these Bylaws, (i) the stockholder must have given timely notice thereof in writing to the Secretary of the corporation, (ii) such other business must be a proper matter for stockholder action under DGCL, (iii) if the stockholder, or the beneficial owner on whose behalf any such proposal or nomination is made, has provided the corporation with a Solicitation Notice (as defined in this Section 5(b)), such stockholder or beneficial owner must, in the case of a proposal, have delivered a proxy statement and form of proxy to holders of at least the percentage of the corporation's voting shares required under applicable law to carry any such proposal, or, in the case of a nomination or nominations, have delivered a proxy statement and form of proxy to holders of a percentage of the corporation's voting shares reasonably believed by such stockholder or beneficial owner to be sufficient to elect the nominee or nominees proposed to be nominated by such stockholder, and must, in either case, have included in such materials the Solicitation Notice, and (iv) if no Solicitation Notice relating thereto has been timely provided pursuant to this section, the stockholder or beneficial owner proposing such business or nomination must not have solicited a number of proxies sufficient to have required the delivery of such a Solicitation Notice under this Section 5. To be timely, a stockholder's notice shall be delivered to the Secretary at the principal executive offices of the Corporation not later than the close of business on the ninetieth (90th) day nor earlier than the close of business on the one hundred twentieth (120th) day prior to the first anniversary of the preceding year's annual meeting; provided, however, that in the event that the date of the annual meeting is advanced more than thirty (30) days prior to or delayed by more than thirty (30) days after the anniversary of the preceding year's annual meeting, notice by the stockholder to be timely must be so delivered not earlier than the close of business on the one hundred twentieth (120th) day prior to such annual meeting and not later than the close of business on the later of the ninetieth (90th) day prior to such annual meeting or the tenth (10th) day following the day on which public announcement of the date of such meeting is first made. In no event shall the public announcement of an adjournment of an annual meeting commence a new time period for the giving of a stockholder's notice as described above. Such stockholder's notice shall set forth: (A) as to each person whom the stockholder proposed to nominate for election or reelection as a director all information relating to such person that is required to be disclosed in solicitations of proxies for election of directors in an election contest, or is otherwise required, in each case pursuant to Regulation 14A under the Securities Exchange Act of 1934, as amended (the "1934 Act") and Rule 14a-11 thereunder (including such person's written consent to being named in the proxy statement as a nominee and to serving as a director if elected); (B) as to any other business that the stockholder proposes to bring before the meeting, a brief description of the business desired to be brought before the meeting, the reasons for conducting such business at the meeting

and any material interest in such business of such stockholder and the beneficial owner, if any, on whose behalf the proposal is made; and (C) as to the stockholder giving the notice and the beneficial owner, if any, on whose behalf the nomination or proposal is made (i) the name and address of such

stockholder, as they appear on the corporation's books, and of such beneficial owner, (ii) the class and number of shares of the corporation which are owned beneficially and of record by such stockholder and such beneficial owner, and (iii) whether either such stockholder or beneficial owner intends to deliver a proxy statement and form of proxy to holders of, in the case of the proposal, at least the percentage of the corporation's voting shares required under applicable law to carry the proposal or, in the case of a nomination or nominations, a sufficient number of holders of the corporation's voting shares to elect such nominee or nominees (an affirmative statement of such intent, a "Solicitation Notice").

(c) Notwithstanding anything in the second sentence of Section 5(b) of these Bylaws to the contrary, in the event that the number of directors to be elected to the Board of Directors of the Corporation is increased and there is no public announcement naming all of the nominees for director or specifying the size of the increased Board of Directors made by the corporation at least one hundred (100) days prior to the first anniversary of the preceding year's annual meeting, a stockholder's notice required by this Section 5 shall also be considered timely, but only with respect to nominees for any new positions created by such increase, if it shall be delivered to the Secretary at the principal executive offices of the corporation not later than the close of business on the tenth (10th) day following the day on which such public announcement is first made by the corporation.

(d) Only such persons who are nominated in accordance with the procedures set forth in this Section 5 shall be eligible to serve as directors and only such business shall be conducted at a meeting of stockholders as shall have been brought before the meeting in accordance with the procedures set forth in this Section 5. Except as otherwise provided by law, the Chairman of the meeting shall have the power and duty to determine whether a nomination or any business proposed to be brought before the meeting was made, or proposed, as the case may be, in accordance with the procedures set forth in these Bylaws and, if any proposed nomination or business is not in compliance with these Bylaws, to declare that such defective proposal or nomination shall not be presented for stockholder action at the meeting and shall be disregarded.

(e) Notwithstanding the foregoing provisions of this Section 5, in order to include information with respect to a stockholder proposal in the proxy statement and form of proxy for a stockholders' meeting, stockholders must provide notice as required by the regulations promulgated under the 1934 Act. Nothing in these Bylaws shall be deemed to affect any rights of stockholders to request inclusion of proposals in the corporation's proxy statement pursuant to Rule 14a-8 under the 1934 Act.

(f) For purposes of this Section 5, "public announcement" shall mean disclosure in a press release reported by the Dow Jones News Service, Associated Press or comparable national news service or in a document publicly filed by the corporation with the Securities and Exchange Commission pursuant to Section 13, 14 or 15(d) of the 1934 Act.

SECTION 6. SPECIAL MEETINGS.

(a) Special meetings of the stockholders of the corporation may be called, for any purpose or purposes, by (i) the Chairman of the Board of Directors, (ii) the Chief Executive Officer, or (iii) the Board of Directors pursuant to a resolution adopted by a majority of the total number of authorized directors (whether or not there exist any vacancies in previously authorized directorships at the time any such resolution is presented to the Board of Directors for adoption).

(b) If a special meeting is properly called by any person or persons other than the Board of Directors, the request shall be in writing, specifying the general nature of the business proposed to be transacted, and shall be delivered personally or sent by certified or registered mail, return receipt requested, to the Chairman of the Board of Directors, the Chief Executive Officer, or the Secretary of the corporation. No business may be transacted at such special meeting otherwise than specified in such notice. The Board of Directors shall determine the time and place of such special meeting, which shall be held not less than thirty-five (35) nor more than one hundred twenty (120) days after the date of the receipt of the request. Upon determination of the time and place of the meeting, the officer receiving the request shall cause notice to be given to the stockholders entitled to vote, in accordance with the provisions of Section 7 of these Bylaws. Nothing contained in this paragraph (b) shall be construed as limiting, fixing, or affecting the time when a meeting of stockholders called by action of the Board of Directors may be held.

(c) Nominations of persons for election to the Board of

Directors may be made at a special meeting of stockholders at which directors are to be elected pursuant to the corporation's notice of meeting (i) by or at the direction of the Board of Directors or (ii) by any stockholder of the corporation who is a stockholder of record at the time of giving notice provided for in these Bylaws who shall be entitled to vote at the meeting and who complies with the notice procedures set forth in this Section 6(c). In the event the corporation calls a special meeting of stockholders for the purpose of electing one or more directors to the Board of Directors, any such stockholder may nominate a person or persons (as the case may be), for election to such position(s) as specified in the corporation's notice of meeting, if the stockholder's notice required by Section 5(b) of these Bylaws shall be delivered to the Secretary at the principal executive offices of the corporation not earlier than the close of business on the one hundred twentieth (120th) day prior to such special meeting and not later than the close of business on the later of the ninetieth (90th) day prior to such meeting or the tenth (10th) day following the day on which public announcement is first made of the date of the special meeting and of the nominees proposed by the Board of Directors to be elected at such meeting. In no event shall the public announcement of an adjournment of a special meeting commence a new time period for the giving of a stockholder's notice as described above.

SECTION 7. NOTICE OF MEETINGS. Except as otherwise provided by law or the Certificate of Incorporation, notice, given in writing or by electronic transmission, of each meeting of stockholders shall be given not less than ten (10) nor more than sixty (60) days before the date of the meeting to each stockholder entitled to vote at such meeting, such notice to specify the place, if any, date and hour and purpose or purposes of the meeting and the means of remote communications, if any, by which stockholders and proxy holders may be deemed to be

present in person and vote at such meeting. Notice of the time, place, if any, and purpose of any meeting of stockholders may be waived in writing, signed by the person entitled to notice thereof, or by electronic transmission by such person, either before or after such meeting, and will be waived by any stockholder by his attendance thereat in person, by remote communication, if applicable, or by proxy, except when the stockholder attends a meeting for the express purpose of objecting, at the beginning of the meeting, to the transaction of any business because the meeting is not lawfully called or convened. Any stockholder so waiving notice of such meeting shall be bound by the proceedings of any such meeting in all respects as if due notice thereof had been given. (Del. Code Ann., tit. 8, Sections 222, 229)

SECTION 8. QUORUM. At all meetings of stockholders, except where otherwise provided by statute or by the Certificate of Incorporation, or by these Bylaws, the presence, in person, by remote communication, if applicable, or by proxy duly authorized, of the holders of a majority of the outstanding shares of stock entitled to vote shall constitute a quorum for the transaction of business. In the absence of a quorum, any meeting of stockholders may be adjourned, from time to time, either by the chairman of the meeting or by vote of the holders of a majority of the shares represented thereat, but no other business shall be transacted at such meeting. The stockholders present at a duly called or convened meeting, at which a quorum is present, may continue to transact business until adjournment, notwithstanding the withdrawal of enough stockholders to leave less than a quorum. Except as otherwise provided by statute or by applicable stock exchange or Nasdaq rules, or by the Certificate of Incorporation or these Bylaws, in all matters other than the election of directors, the affirmative vote of the majority of shares present in person, by remote communication, if applicable, or represented by proxy at the meeting and entitled to vote generally on the subject matter shall be the act of the stockholders. Except as otherwise provided by statute, the Certificate of Incorporation or these Bylaws, directors shall be elected by a plurality of the votes of the shares present in person, by remote communication, if applicable, or represented by proxy at the meeting and entitled to vote generally on the election of directors. Where a separate vote by a class or classes or series is required, except where otherwise provided by the statute or by the Certificate of Incorporation or these Bylaws, a majority of the outstanding shares of such class or classes or series, present in person, by remote communication, if applicable, or represented by proxy duly authorized, shall constitute a quorum entitled to take action with respect to that vote on that matter. Except where otherwise provided by statute or by the Certificate of Incorporation or these Bylaws, the affirmative vote of the majority (plurality, in the case of the election of directors) of shares of such class or classes or series present in person, by remote communication, if applicable, or represented by proxy at the meeting shall be the act of such class or classes or series. (Del. Code Ann., tit. 8, Section 216)

SECTION 9. ADJOURNMENT AND NOTICE OF ADJOURNED MEETINGS. Any meeting of stockholders, whether annual or special, may be adjourned from time to time

either by the chairman of the meeting or by the vote of a majority of the shares present in person, by remote communication, if applicable, or represented by proxy at the meeting. When a meeting is adjourned to another time or place, if any, notice need not be given of the adjourned meeting if the time and place, if any, thereof are announced at the meeting at which the adjournment is taken. At the adjourned meeting, the corporation may transact any business which might have been transacted at the original meeting. If the adjournment is for more than thirty (30) days or if

after the adjournment a new record date is fixed for the adjourned meeting, a notice of the adjourned meeting shall be given to each stockholder of record entitled to vote at the meeting. (Del. Code Ann., tit. 8, Section 222(c))

SECTION 10. VOTING RIGHTS. For the purpose of determining those stockholders entitled to vote at any meeting of the stockholders, except as otherwise provided by law, only persons in whose names shares stand on the stock records of the corporation on the record date, as provided in Section 12 of these Bylaws, shall be entitled to vote at any meeting of stockholders. Every person entitled to vote shall have the right to do so either in person, by remote communication, if applicable, or by an agent or agents authorized by a proxy granted in accordance with Delaware law. An agent so appointed need not be a stockholder. No proxy shall be voted after three (3) years from its date of creation unless the proxy provides for a longer period. (Del. Code Ann., tit. 8, Sections 211(e), 212(b))

SECTION 11. JOINT OWNERS OF STOCK. If shares or other securities having voting power stand of record in the names of two (2) or more persons, whether fiduciaries, members of a partnership, joint tenants, tenants in common, tenants by the entirety, or otherwise, or if two (2) or more persons have the same fiduciary relationship respecting the same shares, unless the Secretary is given written notice to the contrary and is furnished with a copy of the instrument or order appointing them or creating the relationship wherein it is so provided, their acts with respect to voting shall have the following effect: (a) if only one (1) votes, his act binds all; (b) if more than one (1) votes, the act of the majority so voting binds all; (c) if more than one (1) votes, but the vote is evenly split on any particular matter, each faction may vote the securities in question proportionally, or may apply to the Delaware Court of Chancery for relief as provided in the DGCL, Section 217(b). If the instrument filed with the Secretary shows that any such tenancy is held in unequal interests, a majority or even-split for the purpose of subsection (c) shall be a majority or even-split in interest. (Del. Code Ann., tit. 8, Section 217(b))

SECTION 12. LIST OF STOCKHOLDERS. The Secretary shall prepare and make, at least ten (10) days before every meeting of stockholders, a complete list of the stockholders entitled to vote at said meeting, arranged in alphabetical order, showing the address of each stockholder and the number of shares registered in the name of each stockholder. Such list shall be open to the examination of any stockholder, for any purpose germane to the meeting, (a) on a reasonably accessible electronic network, provided that the information required to gain access to such list is provided with the notice of the meeting, or (b) during ordinary business hours, at the principal place of business of the corporation. In the event that the corporation determines to make the list available on an electronic network, the corporation may take reasonable steps to ensure that such information is available only to stockholders of the corporation. The list shall be open to examination of any stockholder during the time of the meeting as provided by law. (Del. Code Ann., tit. 8, Section 219)

SECTION 13. ACTION WITHOUT MEETING.

(a) No action shall be taken by the stockholders except at an annual or special meeting of stockholders called in accordance with these Bylaws, and no action shall be taken by the stockholders by written consent or by electronic transmission.

SECTION 14. ORGANIZATION.

(a) At every meeting of stockholders, the Chairman of the Board of Directors, or, if a Chairman has not been appointed or is absent, the President, or, if the President is absent, a chairman of the meeting chosen by a majority in interest of the stockholders entitled to vote, present in person or by proxy, shall act as chairman. The Secretary, or, in his absence, an Assistant Secretary directed to do so by the President, shall act as secretary of the meeting.

(b) The Board of Directors of the corporation shall be entitled

to make such rules or regulations for the conduct of meetings of stockholders as it shall deem necessary, appropriate or convenient. Subject to such rules and regulations of the Board of Directors, if any, the chairman of the meeting shall have the right and authority to prescribe such rules, regulations and procedures and to do all such acts as, in the judgment of such chairman, are necessary, appropriate or convenient for the proper conduct of the meeting, including, without limitation, establishing an agenda or order of business for the meeting, rules and procedures for maintaining order at the meeting and the safety of those present, limitations on participation in such meeting to stockholders of record of the corporation and their duly authorized and constituted proxies and such other persons as the chairman shall permit, restrictions on entry to the meeting after the time fixed for the commencement thereof, limitations on the time allotted to questions or comments by participants and regulation of the opening and closing of the polls for balloting on matters which are to be voted on by ballot. The date and time of the opening and closing of the polls for each matter upon which the stockholders will vote at the meeting shall be announced at the meeting. Unless and to the extent determined by the Board of Directors or the chairman of the meeting, meetings of stockholders shall not be required to be held in accordance with rules of parliamentary procedure.

ARTICLE IV

DIRECTORS

SECTION 15. NUMBER AND TERM OF OFFICE. The authorized number of directors of the corporation shall be fixed in accordance with the Certificate of Incorporation. Directors need not be stockholders unless so required by the Certificate of Incorporation. If for any cause, the directors shall not have been elected at an annual meeting, they may be elected as soon thereafter as convenient at a special meeting of the stockholders called for that purpose in the manner provided in these Bylaws. (Del. Code Ann., tit. 8, Sections 141(b), 211(b), (c))

SECTION 16. POWERS. The powers of the corporation shall be exercised, its business conducted and its property controlled by the Board of Directors, except as may be otherwise provided by statute or by the Certificate of Incorporation. (Del. Code Ann., tit. 8, Section 141(a))

SECTION 17. CLASSES OF DIRECTORS. Subject to the rights of the holders of any series of Preferred Stock to elect additional directors under specified circumstances, the directors shall be divided into three classes designated as Class I, Class II and Class III, respectively. At the first annual meeting of stockholders following the initial classification of the Board of Directors, the

term of office of the Class I directors shall expire and Class I directors shall be elected for a full term of three years. At the second annual meeting of stockholders following such initial classification, the term of office of the Class II directors shall expire and Class II directors shall be elected for a full term of three years. At the third annual meeting of stockholders following such initial classification, the term of office of the Class III directors shall expire and Class III directors shall be elected for a full term of three years. At each succeeding annual meeting of stockholders, directors shall be elected for a full term of three years to succeed the directors of the class whose terms expire at such annual meeting.

Notwithstanding the foregoing provisions of this section, each director shall serve until his or her successor is duly elected and qualified or until his or her death, resignation or removal. No decrease in the number of directors constituting the Board of Directors shall shorten the term of any incumbent director.

SECTION 18. VACANCIES.

(a) Unless otherwise provided in the Certificate of Incorporation and subject to the rights of the holders of any series of Preferred Stock, any vacancies on the Board of Directors resulting from death, resignation, disqualification, removal or other causes and any newly created directorships resulting from any increase in the number of directors shall, unless the Board of Directors determines by resolution that any such vacancies or newly created directorships shall be filled by stockholders, be filled only by the affirmative vote of a majority of the directors then in office, even though less than a quorum of the Board of Directors. Any director elected in accordance with the preceding sentence shall hold office for the remainder of the full term of the director for which the vacancy was created or occurred and until such director's successor shall have been elected and qualified. A vacancy in the Board of Directors shall be deemed to exist under this Section 18 in the case of the death, removal or resignation of any director. (Del. Code Ann., tit. 8, Section 223(a), (b))

SECTION 19. RESIGNATION. Any director may resign at any time by delivering his or her notice in writing or by electronic transmission to the Secretary, such resignation to specify whether it will be effective at a particular time, upon receipt by the Secretary or at the pleasure of the Board of Directors. If no such specification is made, it shall be deemed effective at the pleasure of the Board of Directors. When one or more directors shall resign from the Board of Directors, effective at a future date, a majority of the directors then in office, including those who have so resigned, shall have power to fill such vacancy or vacancies, the vote thereon to take effect when such resignation or resignations shall become effective, and each Director so chosen shall hold office for the unexpired portion of the term of the Director whose place shall be vacated and until his successor shall have been duly elected and qualified. (Del. Code Ann., tit. 8, Sections 141(b), 223(d))

SECTION 20. MEETINGS.

(a) REGULAR MEETINGS. Unless otherwise restricted by the Certificate of Incorporation, regular meetings of the Board of Directors may be held at any time or date and at any place within or without the State of Delaware which has been designated by the Board of Directors and publicized among all directors, either orally or in writing, by telephone, including

a voice-messaging system or other system designed to record and communicate messages, facsimile, telegraph or telex, or by electronic mail or other electronic means. No further notice shall be required for regular meetings of the Board of Directors. (Del. Code Ann., tit. 8, Section 141(g))

(b) SPECIAL MEETINGS. Unless otherwise restricted by the Certificate of Incorporation, special meetings of the Board of Directors may be held at any time and place within or without the State of Delaware whenever called by the Chairman of the Board, the President or a majority of the authorized number of directors. (Del. Code Ann., tit. 8, Section 141(g))

(c) MEETINGS BY ELECTRONIC COMMUNICATIONS EQUIPMENT. Any member of the Board of Directors, or of any committee thereof, may participate in a meeting by means of conference telephone or other communications equipment by means of which all persons participating in the meeting can hear each other, and participation in a meeting by such means shall constitute presence in person at such meeting. (Del. Code Ann., tit. 8, Section 141(i))

(d) NOTICE OF SPECIAL MEETINGS. Notice of the time and place of all special meetings of the Board of Directors shall be orally or in writing, by telephone, including a voice messaging system or other system or technology designed to record and communicate messages, facsimile, telegraph or telex, or by electronic mail or other electronic means, during normal business hours, at least twenty-four (24) hours before the date and time of the meeting, or sent in writing to each director by first class mail, charges prepaid, at least three (3) days before the date of the meeting. Notice of any meeting may be waived in writing, or by electronic transmission, at any time before or after the meeting and will be waived by any director by attendance thereat, except when the director attends the meeting for the express purpose of objecting, at the beginning of the meeting, to the transaction of any business because the meeting is not lawfully called or convened. (Del. Code Ann., tit. 8, Section 229)

(e) WAIVER OF NOTICE. The transaction of all business at any meeting of the Board of Directors, or any committee thereof, however called or noticed, or wherever held, shall be as valid as though had at a meeting duly held after regular call and notice, if a quorum be present and if, either before or after the meeting, each of the directors not present who did not receive notice shall sign a written waiver of notice or shall waive notice by electronic transmission. All such waivers shall be filed with the corporate records or made a part of the minutes of the meeting. (Del. Code Ann., tit. 8, Section 229)

SECTION 21. QUORUM AND VOTING.

(a) Unless the Certificate of Incorporation requires a greater number, a quorum of the Board of Directors shall consist of a majority of the exact number of directors fixed from time to time by the Board of Directors in accordance with the Certificate of Incorporation; PROVIDED, HOWEVER, at any meeting whether a quorum be present or otherwise, a majority of the directors present may adjourn from time to time until the time fixed for the next regular meeting of the Board of Directors, without notice other than by announcement at the meeting. (Del. Code Ann., tit. 8, Section 141(b))

(b) At each meeting of the Board of Directors at which a quorum is present, all questions and business shall be determined by the affirmative vote of a majority of the directors present, unless a different vote be required by law, the Certificate of Incorporation or these Bylaws. (Del. Code Ann., tit. 8, Section 141(b))

SECTION 22. ACTION WITHOUT MEETING. Unless otherwise restricted by the Certificate of Incorporation or these Bylaws, any action required or permitted to be taken at any meeting of the Board of Directors or of any committee thereof may be taken without a meeting, if all members of the Board of Directors or committee, as the case may be, consent thereto in writing or by electronic transmission, and such writing or writings or transmission or transmissions are filed with the minutes of proceedings of the Board of Directors or committee. Such filing shall be in paper form if the minutes are maintained in paper form and shall be in electronic form if the minutes are maintained in electronic form. (Del. Code Ann., tit. 8, Section 141(f))

SECTION 23. FEES AND COMPENSATION. Directors shall be entitled to such compensation for their services as may be approved by the Board of Directors, including, if so approved, by resolution of the Board of Directors, a fixed sum and expenses of attendance, if any, for attendance at each regular or special meeting of the Board of Directors and at any meeting of a committee of the Board of Directors. Nothing herein contained shall be construed to preclude any director from serving the corporation in any other capacity as an officer, agent, employee, or otherwise and receiving compensation therefor. (Del. Code Ann., tit. 8, Section 141(h))

Section 24. Committees.

(a) EXECUTIVE COMMITTEE. The Board of Directors may appoint an Executive Committee to consist of one (1) or more members of the Board of Directors. The Executive Committee, to the extent permitted by law and provided in the resolution of the Board of Directors shall have and may exercise all the powers and authority of the Board of Directors in the management of the business and affairs of the corporation, and may authorize the seal of the corporation to be affixed to all papers which may require it; but no such committee shall have the power or authority in reference to (i) approving or adopting, or recommending to the stockholders, any action or matter expressly required by the DGCL to be submitted to stockholders for approval, or (ii) adopting, amending or repealing any bylaw of the corporation. (Del. Code Ann., tit. 8, Section 141(c))

(b) OTHER COMMITTEES. The Board of Directors may, from time to time, appoint such other committees as may be permitted by law. Such other committees appointed by the Board of Directors shall consist of one (1) or more members of the Board of Directors and shall have such powers and perform such duties as may be prescribed by the resolution or resolutions creating such committees, but in no event shall any such committee have the powers denied to the Executive Committee in these Bylaws. (Del. Code Ann., tit. 8, Section 141(c))

(c) TERM. The Board of Directors, subject to any requirements of any outstanding series of Preferred Stock and the provisions of subsections (a) or (b) of this Bylaw, may at any time increase or decrease the number of members of a committee or terminate the existence of a committee. The membership of a committee member shall terminate on the date of his or her death or voluntary resignation from the committee or from the Board of Directors.

The Board of Directors may at any time for any reason remove any individual committee member and the Board of Directors may fill any committee vacancy created by death, resignation, removal or increase in the number of members of the committee. The Board of Directors may designate one or more directors as alternate members of any committee, who may replace any absent or disqualified member at any meeting of the committee, and, in addition, in the absence or disqualification of any member of a committee, the member or members thereof present at any meeting and not disqualified from voting, whether or not he or they constitute a quorum, may unanimously appoint another member of the Board of Directors to act at the meeting in the place of any such absent or disqualified member. (Del. Code Ann., tit. 8, Section 141(c))

(d) MEETINGS. Unless the Board of Directors shall otherwise provide, regular meetings of the Executive Committee or any other committee appointed pursuant to this Section 24 shall be held at such times and places as are determined by the Board of Directors, or by any such committee, and when notice thereof has been given to each member of such committee, no further notice of such regular meetings need be given thereafter. Special meetings of any such committee may be held at any place which has been determined from time to time by such committee, and may be called by any Director who is a member of such committee, upon notice to the members of such committee of the time and

place of such special meeting given in the manner provided for the giving of notice to members of the Board of Directors of the time and place of special meetings of the Board of Directors. Notice of any special meeting of any committee may be waived in writing at any time before or after the meeting and will be waived by any director by attendance thereat, except when the director attends such special meeting for the express purpose of objecting, at the beginning of the meeting, to the transaction of any business because the meeting is not lawfully called or convened. Unless otherwise provided by the Board of Directors in the resolutions authorizing the creation of the committee, a majority of the authorized number of members of any such committee shall constitute a quorum for the transaction of business, and the act of a majority of those present at any meeting at which a quorum is present shall be the act of such committee. (Del. Code Ann., tit. 8, Sections 141(c), 229)

SECTION 25. ORGANIZATION. At every meeting of the directors, the Chairman of the Board of Directors, or, if a Chairman has not been appointed or is absent, the President (if a director), or if the President is absent, the most senior Vice President (if a director), or, in the absence of any such person, a chairman of the meeting chosen by a majority of the directors present, shall preside over the meeting. The Secretary, or in his or her absence, any Assistant Secretary directed to do so by the President, shall act as secretary of the meeting.

ARTICLE V

OFFICERS

SECTION 26. OFFICERS DESIGNATED. The officers of the corporation shall include, if and when designated by the Board of Directors, the Chairman of the Board of Directors, the Chief Executive Officer, the President, one or more Vice Presidents, the Secretary, the Chief Financial Officer, the Treasurer and the Controller, all of whom shall be elected at the annual organizational meeting of the Board of Directors. The Board of Directors may also appoint one or more Assistant Secretaries, Assistant Treasurers, Assistant Controllers and such other officers

and agents with such powers and duties as it shall deem necessary. The Board of Directors may assign such additional titles to one or more of the officers as it shall deem appropriate. Any one person may hold any number of offices of the corporation at any one time unless specifically prohibited therefrom by law. The salaries and other compensation of the officers of the corporation shall be fixed by or in the manner designated by the Board of Directors. (Del. Code Ann., tit. 8, Sections 122(5), 142(a), (b))

SECTION 27. TENURE AND DUTIES OF OFFICERS.

(a) GENERAL. All officers shall hold office at the pleasure of the Board of Directors and until their successors shall have been duly elected and qualified, unless sooner removed. Any officer elected or appointed by the Board of Directors may be removed at any time by the Board of Directors. If the office of any officer becomes vacant for any reason, the vacancy may be filled by the Board of Directors. (Del. Code Ann., tit. 8, Section 141(b), (e))

(b) DUTIES OF CHAIRMAN OF THE BOARD OF DIRECTORS. The Chairman of the Board of Directors, when present, shall preside at all meetings of the stockholders and the Board of Directors. The Chairman of the Board of Directors shall perform other duties commonly incident to the office and shall also perform such other duties and have such other powers, as the Board of Directors shall designate from time to time. If there is no President, then the Chairman of the Board of Directors shall also serve as the Chief Executive Officer of the corporation and shall have the powers and duties prescribed in paragraph (c) of this Section 28. (Del. Code Ann., tit. 8, Section 142(a))

(c) DUTIES OF PRESIDENT. The President shall preside at all meetings of the stockholders and at all meetings of the Board of Directors, unless the Chairman of the Board of Directors has been appointed and is present. Unless some other officer has been elected Chief Executive Officer of the corporation, the President shall be the chief executive officer of the corporation and shall, subject to the control of the Board of Directors, have general supervision, direction and control of the business and officers of the corporation. The President shall perform other duties commonly incident to the office and shall also perform such other duties and have such other powers, as the Board of Directors shall designate from time to time. (Del. Code Ann., Tit. 8, Section 142(a))

(d) DUTIES OF EXECUTIVE VICE PRESIDENT AND VICE PRESIDENTS. The Executive Vice President may assume and perform the duties of the President in the absence or disability of the President or whenever the office of President

is vacant. The Executive Vice President and Vice Presidents shall perform other duties commonly incident to their office and shall also perform such other duties and have such other powers as the Board of Directors or the President shall designate from time to time. (Del. Code Ann., tit. 8, Section 142(a))

(e) DUTIES OF SECRETARY. The Secretary shall attend all meetings of the stockholders and of the Board of Directors and shall record all acts and proceedings thereof in the minute book of the corporation. The Secretary shall give notice in conformity with these Bylaws of all meetings of the stockholders and of all meetings of the Board of Directors and any committee thereof requiring notice. The Secretary shall perform all other duties provided for in these Bylaws and other duties commonly incident to the office and shall also perform such other

duties and have such other powers, as the Board of Directors shall designate from time to time. The President may direct any Assistant Secretary to assume and perform the duties of the Secretary in the absence or disability of the Secretary, and each Assistant Secretary shall perform other duties commonly incident to the office and shall also perform such other duties and have such other powers as the Board of Directors or the President shall designate from time to time. (Del. Code Ann., tit. 8, Section 142(a))

(f) DUTIES OF CHIEF FINANCIAL OFFICER. The Chief Financial Officer shall keep or cause to be kept the books of account of the corporation in a thorough and proper manner and shall render statements of the financial affairs of the corporation in such form and as often as required by the Board of Directors or the President. The Chief Financial Officer, subject to the order of the Board of Directors, shall have the custody of all funds and securities of the corporation. The Chief Financial Officer shall perform other duties commonly incident to the office and shall also perform such other duties and have such other powers as the Board of Directors or the President shall designate from time to time. The President may direct the Treasurer or any Assistant Treasurer, or the Controller or any Assistant Controller to assume and perform the duties of the Chief Financial Officer in the absence or disability of the Chief Financial Officer, and each Treasurer and Assistant Treasurer and each Controller and Assistant Controller shall perform other duties commonly incident to the office and shall also perform such other duties and have such other powers as the Board of Directors or the President shall designate from time to time. (Del. Code Ann., tit. 8, Section 142(a))

SECTION 28. DELEGATION OF AUTHORITY. The Board of Directors may from time to time delegate the powers or duties of any officer to any other officer or agent, notwithstanding any provision hereof.

SECTION 29. RESIGNATIONS. Any officer may resign at any time by giving notice in writing or by electronic transmission to the Board of Directors or to the President or to the Secretary. Any such resignation shall be effective when received by the person or persons to whom such notice is given, unless a later time is specified therein, in which event the resignation shall become effective at such later time. Unless otherwise specified in such notice, the acceptance of any such resignation shall not be necessary to make it effective. Any resignation shall be without prejudice to the rights, if any, of the corporation under any contract with the resigning officer. (Del. Code Ann., tit. 8, Section 142(b))

SECTION 30. REMOVAL. Any officer may be removed from office at any time, either with or without cause, by the affirmative vote of a majority of the directors in office at the time, or by the unanimous written consent of the directors in office at the time, or by any committee or superior officers upon whom such power of removal may have been conferred by the Board of Directors.

ARTICLE VI

EXECUTION OF CORPORATE INSTRUMENTS AND VOTING OF SECURITIES OWNED BY THE CORPORATION

SECTION 31. EXECUTION OF CORPORATE INSTRUMENTS. The Board of Directors may, in its discretion, determine the method and designate the signatory officer or officers, or other person or persons, to execute on behalf of the corporation any corporate instrument or document, or to sign on behalf of the corporation the corporate name without limitation, or to enter into contracts on behalf of the corporation, except where otherwise provided by law or these Bylaws, and such execution or signature shall be binding upon the corporation. (Del. Code Ann., tit. 8, Sections 103(a), 142(a), 158)

All checks and drafts drawn on banks or other depositaries on funds to the credit of the corporation or in special accounts of the corporation shall be signed by such person or persons as the Board of Directors shall authorize so to do.

Unless authorized or ratified by the Board of Directors or within the agency power of an officer, no officer, agent or employee shall have any power or authority to bind the corporation by any contract or engagement or to pledge its credit or to render it liable for any purpose or for any amount. (Del. Code Ann., tit. 8, Sections 103(a), 142(a), 158).

SECTION 32. VOTING OF SECURITIES OWNED BY THE CORPORATION. All stock and other securities of other corporations owned or held by the corporation for itself, or for other parties in any capacity, shall be voted, and all proxies with respect thereto shall be executed, by the person authorized so to do by resolution of the Board of Directors, or, in the absence of such authorization, by the Chairman of the Board of Directors, the Chief Executive Officer, the President, or any Vice President. (Del. Code Ann., tit. 8, Section 123)

ARTICLE VII

SHARES OF STOCK

SECTION 33. FORM AND EXECUTION OF CERTIFICATES. Certificates for the shares of stock of the corporation shall be in such form as is consistent with the Certificate of Incorporation and applicable law. Every holder of stock in the corporation shall be entitled to have a certificate signed by or in the name of the corporation by the Chairman of the Board of Directors, or the President or any Vice President and by the Treasurer or Assistant Treasurer or the Secretary or Assistant Secretary, certifying the number of shares owned by such stockholder in the corporation. Any or all of the signatures on the certificate may be facsimiles. In case any officer, transfer agent, or registrar who has signed or whose facsimile signature has been placed upon a certificate shall have ceased to be such officer, transfer agent, or registrar before such certificate is issued, it may be issued with the same effect as if he were such officer, transfer agent, or registrar at the date of issue. Each certificate shall state upon the face or back thereof, in full or in summary, all of the powers, designations, preferences, and rights, and the limitations or restrictions of the shares authorized to be issued or shall, except as otherwise required by law, set forth on the face or back a statement that the corporation will furnish without charge to each

stockholder who so requests the powers, designations, preferences and relative, participating, optional, or other special rights of each class of stock or series thereof and the qualifications, limitations or restrictions of such preferences and/or rights. Within a reasonable time after the issuance or transfer of uncertificated stock, the corporation shall send to the registered owner thereof a written notice containing the information required to be set forth or stated on certificates pursuant to this section or otherwise required by law or with respect to this section a statement that the corporation will furnish without charge to each stockholder who so requests the powers, designations, preferences and relative participating, optional or other special rights of each class of stock or series thereof and the qualifications, limitations or restrictions of such preferences and/or rights. (Del. Code Ann., tit. 8, Section 158)

SECTION 34. LOST CERTIFICATES. A new certificate or certificates shall be issued in place of any certificate or certificates theretofore issued by the corporation alleged to have been lost, stolen, or destroyed, upon the making of an affidavit of that fact by the person claiming the certificate of stock to be lost, stolen, or destroyed. The corporation may require, as a condition precedent to the issuance of a new certificate or certificates, the owner of such lost, stolen, or destroyed certificate or certificates, or the owner's legal representative, to agree to indemnify the corporation in such manner as it shall require or to give the corporation a surety bond in such form and amount as it may direct as indemnity against any claim that may be made against the corporation with respect to the certificate alleged to have been lost, stolen, or destroyed. (Del. Code Ann., tit. 8, Section 167)

SECTION 35. TRANSFERS.

(a) Transfers of record of shares of stock of the corporation shall be made only upon its books by the holders thereof, in person or by attorney duly authorized, and upon the surrender of a properly endorsed certificate or certificates for a like number of shares. (Del. Code Ann., tit. 8, Section 201, tit. 6, Section 8- 401(1))

(b) The corporation shall have power to enter into and perform

any agreement with any number of stockholders of any one or more classes of stock of the corporation to restrict the transfer of shares of stock of the corporation of any one or more classes owned by such stockholders in any manner not prohibited by the DGCL. (Del. Code Ann., tit. 8, Section 160 (a))

SECTION 36. FIXING RECORD DATES.

(a) In order that the corporation may determine the stockholders entitled to notice of or to vote at any meeting of stockholders or any adjournment thereof, the Board of Directors may fix, in advance, a record date, which record date shall not precede the date upon which the resolution fixing the record date is adopted by the Board of Directors, and which record date shall, subject to applicable law, not be more than sixty (60) nor less than ten (10) days before the date of such meeting. If no record date is fixed by the Board of Directors, the record date for determining stockholders entitled to notice of or to vote at a meeting of stockholders shall be at the close of business on the day next preceding the day on which notice is given, or if notice is waived, at the close of business on the day next preceding the day on which the meeting is held. A determination of stockholders of record entitled to notice of or to

vote at a meeting of stockholders shall apply to any adjournment of the meeting; provided, however, that the Board of Directors may fix a new record date for the adjourned meeting.

(b) In order that the corporation may determine the stockholders entitled to receive payment of any dividend or other distribution or allotment of any rights or the stockholders entitled to exercise any rights in respect of any change, conversion or exchange of stock, or for the purpose of any other lawful action, the Board of Directors may fix, in advance, a record date, which record date shall not precede the date upon which the resolution fixing the record date is adopted, and which record date shall be not more than sixty (60) days prior to such action. If no record date is fixed, the record date for determining stockholders for any such purpose shall be at the close of business on the day on which the Board of Directors adopts the resolution relating thereto. (Del. Code Ann., tit. 8, Section 213)

SECTION 37. REGISTERED STOCKHOLDERS. The corporation shall be entitled to recognize the exclusive right of a person registered on its books as the owner of shares to receive dividends, and to vote as such owner, and shall not be bound to recognize any equitable or other claim to or interest in such share or shares on the part of any other person whether or not it shall have express or other notice thereof, except as otherwise provided by the laws of Delaware. (Del. Code Ann., tit. 8, Sections 213(a), 219)

ARTICLE VIII

OTHER SECURITIES OF THE CORPORATION

SECTION 38. EXECUTION OF OTHER SECURITIES. All bonds, debentures and other corporate securities of the corporation, other than stock certificates (covered in Section 33), may be signed by the Chairman of the Board of Directors, the President or any Vice President, or such other person as may be authorized by the Board of Directors, and the corporate seal impressed thereon or a facsimile of such seal imprinted thereon and attested by the signature of the Secretary or an Assistant Secretary, or the Chief Financial Officer or Treasurer or an Assistant Treasurer; PROVIDED, HOWEVER, that where any such bond, debenture or other corporate security shall be authenticated by the manual signature, or where permissible by applicable law, facsimile signature, of a trustee under an indenture pursuant to which such bond, debenture or other corporate security shall be issued, the signatures of the persons signing and attesting the corporate seal on such bond, debenture or other corporate security may be the imprinted facsimile of the signatures of such persons. Interest coupons appertaining to any such bond, debenture or other corporate security, authenticated by a trustee as aforesaid, shall be signed by the Treasurer or an Assistant Treasurer of the corporation or such other person as may be authorized by the Board of Directors, or bear imprinted thereon the facsimile signature of such person. In case any officer who shall have signed or attested any bond, debenture or other corporate security, or whose facsimile signature shall appear thereon or on any such interest coupon, shall have ceased to be such officer before the bond, debenture or other corporate security so signed or attested shall have been delivered, such bond, debenture or other corporate security nevertheless may be adopted by the corporation and issued and delivered as though the person who signed the same or whose facsimile signature shall have been used thereon had not ceased to be such officer of the corporation.

ARTICLE IX

DIVIDENDS

SECTION 39. DECLARATION OF DIVIDENDS. Dividends upon the capital stock of the corporation, subject to the provisions of the Certificate of Incorporation and applicable law, if any, may be declared by the Board of Directors pursuant to law at any regular or special meeting. Dividends may be paid in cash, in property, or in shares of the capital stock, subject to the provisions of the Certificate of Incorporation and applicable law. (Del. Code Ann., tit. 8, Sections 170, 173)

SECTION 40. DIVIDEND RESERVE. Before payment of any dividend, there may be set aside out of any funds of the corporation available for dividends such sum or sums as the Board of Directors from time to time, in their absolute discretion, think proper as a reserve or reserves to meet contingencies, or for equalizing dividends, or for repairing or maintaining any property of the corporation, or for such other purpose as the Board of Directors shall think conducive to the interests of the corporation, and the Board of Directors may modify or abolish any such reserve in the manner in which it was created. (Del. Code Ann., tit. 8, Section 171)

ARTICLE X

FISCAL YEAR

SECTION 41. FISCAL YEAR. The fiscal year of the corporation shall be fixed by resolution of the Board of Directors.

ARTICLE XI

INDEMNIFICATION

SECTION 42. INDEMNIFICATION OF DIRECTORS, EXECUTIVE OFFICERS, OTHER OFFICERS, EMPLOYEES AND OTHER AGENTS.

(A) DIRECTORS AND EXECUTIVE OFFICERS. The corporation shall indemnify its directors and executive officers (for the purposes of this Article XI, "executive officers" shall have the meaning defined in Rule 3b-7 promulgated under the 1934 Act) to the fullest extent not prohibited by the DGCL or any other applicable law; PROVIDED, HOWEVER, that the corporation may modify the extent of such indemnification by individual contracts with its directors and executive officers; and, PROVIDED, FURTHER, that the corporation shall not be required to indemnify any director or executive officer in connection with any proceeding (or part thereof) initiated by such person unless (i) such indemnification is expressly required to be made by law, (ii) the proceeding was authorized by the Board of Directors of the corporation, (iii) such indemnification is provided by the corporation, in its sole discretion, pursuant to the powers vested in the corporation under the DGCL or any other applicable law or (iv) such indemnification is required to be made under subsection (d).

(b) OTHER OFFICERS, EMPLOYEES AND OTHER AGENTS. The corporation shall have power to indemnify its other officers, employees and other agents as set forth in the DGCL or any other applicable law. The Board of Directors shall have the power to delegate the determination of whether indemnification shall be given to any such person to such officers or other persons as the Board of Directors shall determine.

(c) EXPENSES. The corporation shall advance to any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative, by reason of the fact that he or she is or was a director or executive officer of the corporation, or is or was serving at the request of the corporation as a director or executive officer of another corporation, partnership, joint venture, trust or other enterprise, prior to the final disposition of the proceeding, promptly following request therefor, all expenses incurred by any director or executive officer in connection with such proceeding provided, however, that if the DGCL requires, an advancement of expenses incurred by a director or executive officer in his or her capacity as a director or executive officer (and not in any other capacity in which service was or is rendered by such indemnitee, including, without limitation, service to an employee benefit plan) shall be made only upon delivery to the corporation of an undertaking (hereinafter an "undertaking"), by or on behalf of such indemnitee, to repay all amounts so advanced if it shall ultimately be determined by final judicial decision from which there is no further right to appeal (hereinafter a

"final adjudication") that such indemnitee is not entitled to be indemnified for such expenses under this Section 42 or otherwise.

Notwithstanding the foregoing, unless otherwise determined pursuant to paragraph (e) of this Section 42, no advance shall be made by the corporation to an officer of the corporation (except by reason of the fact that such officer is or was a director of the corporation in which event this paragraph shall not apply) in any action, suit or proceeding, whether civil, criminal, administrative or investigative, if a determination is reasonably and promptly made (i) by a majority vote of directors who were not parties to the proceeding, even if not a quorum, or (ii) by a committee of such directors designated by a majority vote of such directors, even though less than a quorum, or (iii) if there are no such directors, or such directors so direct, by independent legal counsel in a written opinion, that the facts known to the decision-making party at the time such determination is made demonstrate clearly and convincingly that such person acted in bad faith or in a manner that such person did not believe to be in or not opposed to the best interests of the corporation.

(d) ENFORCEMENT. Without the necessity of entering into an express contract, all rights to indemnification and advances to directors and executive officers under this Bylaw shall be deemed to be contractual rights and be effective to the same extent and as if provided for in a contract between the corporation and the director or executive officer. Any right to indemnification or advances granted by this Section 42 to a director or executive officer shall be enforceable by or on behalf of the person holding such right in any court of competent jurisdiction if (i) the claim for indemnification or advances is denied, in whole or in part, or (ii) no disposition of such claim is made within ninety (90) days of request therefor. The claimant in such enforcement action, if successful in whole or in part, shall be entitled to be paid also the expense of prosecuting the claim. In connection with any claim for indemnification, the

corporation shall be entitled to raise as a defense to any such action that the claimant has not met the standards of conduct that make it permissible under the DGCL or any other applicable law for the corporation to indemnify the claimant for the amount claimed. Neither the failure of the corporation (including its Board of Directors, independent legal counsel or its stockholders) to have made a determination prior to the commencement of such action that indemnification of the claimant is proper in the circumstances because the claimant has met the applicable standard of conduct set forth in the DGCL or any other applicable law, nor an actual determination by the corporation (including its Board of Directors, independent legal counsel or its stockholders) that the claimant has not met such applicable standard of conduct, shall be a defense to the action or create a presumption that claimant has not met the applicable standard of conduct.

(e) NON-EXCLUSIVITY OF RIGHTS. The rights conferred on any person by this Bylaw shall not be exclusive of any other right which such person may have or hereafter acquire under any applicable statute, provision of the Certificate of Incorporation, Bylaws, agreement, vote of stockholders or disinterested directors or otherwise, both as to action in his official capacity and as to action in another capacity while holding office. The corporation is specifically authorized to enter into individual contracts with any or all of its directors, officers, employees or agents respecting indemnification and advances, to the fullest extent not prohibited by the DGCL, or by any other applicable law.

(f) SURVIVAL OF RIGHTS. The rights conferred on any person by this Bylaw shall continue as to a person who has ceased to be a director, executive officer, officer, employee or other agent and shall inure to the benefit of the heirs, executors and administrators of such a person.

(g) INSURANCE. To the fullest extent permitted by the DGCL or any other applicable law, the corporation, upon approval by the Board of Directors, may purchase insurance on behalf of any person required or permitted to be indemnified pursuant to this Section 42.

(h) AMENDMENTS. Any repeal or modification of this Section 42 shall only be prospective and shall not affect the rights under this Bylaw in effect at the time of the alleged occurrence of any action or omission to act that is the cause of any proceeding against any agent of the corporation.

(i) SAVING CLAUSE. If this Bylaw or any portion hereof shall be invalidated on any ground by any court of competent jurisdiction, then the corporation shall nevertheless indemnify each director and executive officer to the full extent not prohibited by any applicable portion of this Section 42 that shall not have been invalidated, or by any other applicable law. If this Section 42 shall be invalid due to the application of the indemnification provisions of another jurisdiction, then the corporation shall indemnify each director and

executive officer to the full extent under any other applicable law.

(j) CERTAIN DEFINITIONS. For the purposes of this Bylaw, the following definitions shall apply:

(1) The term "proceeding" shall be broadly construed and shall include, without limitation, the investigation, preparation, prosecution, defense, settlement, arbitration and appeal of, and the giving of testimony in, any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative.

(2) The term "expenses" shall be broadly construed and shall include, without limitation, court costs, attorneys' fees, witness fees, fines, amounts paid in settlement or judgment and any other costs and expenses of any nature or kind incurred in connection with any proceeding.

(3) The term the "corporation" shall include, in addition to the resulting corporation, any constituent corporation (including any constituent of a constituent) absorbed in a consolidation or merger which, if its separate existence had continued, would have had power and authority to indemnify its directors, officers, and employees or agents, so that any person who is or was a director, officer, employee or agent of such constituent corporation, or is or was serving at the request of such constituent corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, shall stand in the same position under the provisions of this Section 42 with respect to the resulting or surviving corporation as he or she would have with respect to such constituent corporation if its separate existence had continued.

(4) References to a "director," "executive officer," "officer," "employee," or "agent" of the corporation shall include, without limitation, situations where such person is serving at the request of the corporation as, respectively, a director, executive officer, officer, employee, trustee or agent of another corporation, partnership, joint venture, trust or other enterprise.

(5) References to "other enterprises" shall include employee benefit plans; references to "fines" shall include any excise taxes assessed on a person with respect to an employee benefit plan; and references to "serving at the request of the corporation" shall include any service as a director, officer, employee or agent of the corporation which imposes duties on, or involves services by, such director, officer, employee, or agent with respect to an employee benefit plan, its participants, or beneficiaries; and a person who acted in good faith and in a manner he or she reasonably believed to be in the interest of the participants and beneficiaries of an employee benefit plan shall be deemed to have acted in a manner "not opposed to the best interests of the corporation" as referred to in this Section 42.

ARTICLE XII

NOTICES

SECTION 43. NOTICES.

(a) NOTICE TO STOCKHOLDERS. Whenever, under any provisions of these Bylaws, notice is required to be given to any stockholder, it shall be given in writing, timely and duly deposited in the United States mail, postage prepaid, and addressed to the stockholder's last known post office address as shown by the stock record of the corporation or its transfer agent.

Notice by electronic transmission may be given as provided in the DGCL. (Del. Code Ann., tit. 8, Section 222)

(b) NOTICE TO DIRECTORS. Any notice required to be given to any director may be given by the method stated in subsection (a), or by overnight delivery service, facsimile, telex or telegram, except that such notice other than one which is delivered personally shall be sent to such address as such director shall have filed in writing with the Secretary, or, in the absence of such filing, to the last known post office address of such director.

(c) AFFIDAVIT OF MAILING. An affidavit of mailing, executed by a duly authorized and competent employee of the corporation, its transfer agent or another agent appointed with respect to the class of stock affected, specifying the name and address or the names and addresses of the stockholder or stockholders, or director or directors, to whom any such notice or notices was or were given, and the time and method of giving the same, shall in the absence

of fraud, be prima facie evidence of the facts therein contained. (Del. Code Ann., tit. 8, Section 222)

(d) METHODS OF NOTICE. It shall not be necessary that the same method of giving notice be employed in respect of all recipients of notice, but one permissible method may be employed in respect of any one or more, and any other permissible method or methods may be employed in respect of any other or others.

(e) NOTICE TO PERSON WITH WHOM COMMUNICATION IS UNLAWFUL. Whenever notice is required to be given, under any provision of law or of the Certificate of Incorporation or Bylaws of the corporation, to any person with whom communication is unlawful, the giving of such notice to such person shall not be required and there shall be no duty to apply to any governmental authority or agency for a license or permit to give such notice to such person. Any action or meeting which shall be taken or held without notice to any such person with whom communication is unlawful shall have the same force and effect as if such notice had been duly given. In the event that the action taken by the corporation is such as to require the filing of a certificate under any provision of the DGCL, the certificate shall state, if such is the fact and if notice is required, that notice was given to all persons entitled to receive notice except such persons with whom communication is unlawful.

ARTICLE XIII

AMENDMENTS

SECTION 44. AMENDMENTS. The Board of Directors is expressly empowered to adopt, amend or repeal the Bylaws of the corporation. The stockholders shall also have power to adopt, amend or repeal the Bylaws of the corporation; provided, however, that, in addition to any vote of the holders of any class or series of stock of the corporation required by law or by the Certificate of Incorporation, the affirmative vote of the holders of at least sixty-six and two-thirds percent (66-2/3%) of the voting power of all of the then-outstanding shares of the capital stock of the corporation entitled to vote generally in the election of directors, voting together as a single class, shall be required to adopt, amend or repeal any provision of the Bylaws of the corporation.

ARTICLE XIV

LOANS TO OFFICERS

SECTION 45. LOANS TO OFFICERS. The corporation may lend money to, or guarantee any obligation of, or otherwise assist any officer or other employee of the corporation or of its subsidiaries, including any officer or employee who is a Director of the corporation or its subsidiaries, whenever, in the judgment of the Board of Directors, such loan, guarantee or assistance may reasonably be expected to benefit the corporation. The loan, guarantee or other assistance may be with or without interest and may be unsecured, or secured in such manner as the Board of Directors shall approve, including, without limitation, a pledge of shares of stock of the corporation. Nothing in these Bylaws shall be deemed to deny, limit or restrict the powers of guaranty or warranty of the corporation at common law or under any statute. (Del. Code Ann., tit. 8, Section 143)

CERTIFICATE OF AMENDMENT OF
RESTATED CERTIFICATE OF INCORPORATION OF
ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc., a corporation organized and existing under and by virtue of the General Corporation Law of the State of Delaware, does hereby certify:

FIRST: The name of the Corporation is Isis Pharmaceuticals, Inc. (the "Corporation").

SECOND: The date on which the Corporation's original Certificate of Incorporation was filed with the Secretary of State of the State of Delaware is March 25, 1991.

THIRD: The Board of Directors of the Corporation, acting in accordance with the provisions of Sections 141 and 242 of the General Corporation Law of the State of Delaware, adopted resolutions at a meeting held on December 8, 2000 to amend Article V of the Restated Certificate of Incorporation of the Corporation to read in its entirety as follows:

> The Corporation is authorized to issue two classes of shares designated respectively "Common Stock" and "Preferred Stock." The total number of shares of all classes of stock which the Corporation has authority to issue is 115,000,000 shares, consisting of 100,000,000 shares of Common Stock, each having a par value of $.001, and 15,000,000 shares of Preferred Stock, each having a par value of $.001. The Preferred Stock may be issued in one or more series. The Board of Directors is authorized to fix the number of shares of any such series of Preferred Stock and to determine the designation of any such series (a "Preferred Stock Designation"), subject to (a) such stockholder approvals as may be provided for herein and (b) the number of shares of Preferred Stock authorized at that time by this Article V. Subject to such stockholder approvals as may be provided for herein, the Board of Directors is further authorized to determine or alter the rights, preferences, privileges and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to increase or decrease (but not below the number of shares of such series then outstanding) the number of shares of any series of Preferred Stock. In case the number of shares of any series shall be so decreased, the shares constituting such decrease shall resume the status that they had prior to the adoption of the resolution or amendment originally fixing the number of shares of such series.

FOURTH: The foregoing amendment was submitted to the stockholders of the Corporation for their approval and was duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this Certificate of Amendment to be signed by its duly authorized officers this 9th day of April, 2001.

By: /s/ Stanley T. Crooke

Stanley T. Crooke
Chairman of the Board of Directors
and Chief Executive Officer

*Text Omitted and Filed Separately
Confidential Treatment Requested
Under 17 C.F.R. Sections 200.80(b)(4)
200.83 and 240.24b-2

DEVELOPMENT AND LICENSE AGREEMENT

between

MERCK & CO., INC.

and

ISIS PHARMACEUTICALS, INC.

DEVELOPMENT AND LICENSE AGREEMENT

THIS AGREEMENT is effective as the date of the last party to sign this Agreement (the "Effective Date") between MERCK & CO., INC., a corporation organized and existing under the laws of the State of New Jersey ("MERCK") and ISIS PHARMACEUTICALS, INC. a corporation organized and existing under the laws of the State of Delaware ("ISIS").

RECITALS:

WHEREAS, ISIS has rights in and to ISIS Know-How and ISIS Patent Rights (as the foregoing are hereinafter defined); and,

WHEREAS, MERCK and ISIS desire to enter into an agreement to develop Compound (as hereinafter defined) upon the terms and conditions set forth herein; and,

WHEREAS, MERCK desires to obtain licenses under the ISIS Patent Rights and ISIS Know-How, and the technical assistance of ISIS for the purpose of preparing and manufacturing Compound and Product, upon the terms and conditions set forth herein, and ISIS desires to grant such licenses and such assistance to MERCK.

NOW, THEREFORE, in consideration of the foregoing premises and the mutual covenants herein contained, the parties hereby agree as follows:

ARTICLE I

DEFINITIONS

Unless specifically set forth to the contrary herein, the following terms, whether used in the singular or plural, shall have the respective meanings set forth below:

1.1 "Affiliate" shall mean (i) any corporation or business entity of which fifty percent (50%) or more of the securities or other ownership interests representing the equity, the voting stock or general partnership interest are owned, controlled or held, directly or indirectly, by MERCK or ISIS; or (ii) any corporation or business entity which, directly or indirectly, owns, controls or holds fifty percent (50%) (or the maximum ownership interest permitted by law) or more of the securities or other ownership interests representing the equity, the voting stock or, if applicable, the general partnership interest, of MERCK or ISIS; or (iii) any corporation or business entity of which fifty percent (50%) or more of the securities or other ownership interests representing the equity, the voting stock or general partnership interest are owned, controlled or held, directly or indirectly, by a corporation or business entity described in (i) or (ii).

1.2 "Calendar Quarter" shall mean the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 and December 31.

1.3 "Calendar Year" shall mean each successive period of twelve (12) months commencing on January 1 and ending on December 31.

1.4 "Clinical Development Program" shall mean the clinical development activities undertaken by MERCK as set forth in Article II herein

1.5 "Clinical Supply Agreement" shall mean the Clinical Supply Agreement entered into by the parties on the Effective Date in the form attached hereto as Schedule 1.

1.6 "Combination Product" shall mean a Product which includes one or more pharmaceutically active ingredients other than Compound in combination with Compound. All references to Product in this Agreement shall be deemed to include Combination Product.

1.7 "Compound" shall mean ISIS compounds ISIS 113715 and [*] that, as of the Effective Date and during the term of this Agreement, i) incorporate ISIS Core Technology and ii) target the genetic sequence of PTP-1B thereby reducing expression of PTP-1B protein in humans or animals.

1.8 "Compound Improvement" shall mean any and all enhancements, whether or not patentable, in the Compound. Compound Improvement shall include without limitation pharmaceutical formulations and dosage forms for administration discovered or invented solely or jointly by employees of MERCK, or acquired by MERCK, during the term of this Agreement. Compound Improvement shall not include pharmaceutical formulations or dosage forms for administration discovered or invented solely by employees of ISIS, or acquired by ISIS, during the term of this Agreement.

1.9 "Core Technology Improvement" shall mean any and all enhancements, whether or not patentable, in the ISIS Core Technology arising during the term of this Agreement.

1.10 "Field" shall mean the use of Compound and Product for any and all purposes.

1.11 "First Commercial Sale" shall mean, with respect to any Product, the first sale for end use or consumption of such Product in a country after all required approvals, including marketing and pricing approvals, have been granted by the governing Regulatory Authority of such country.

1.12 "FTE" shall mean the equivalent of a full-time scientist's work time over a twelve-month period (including normal vacations, sick days and holidays). The portion of an FTE year devoted by a scientist to the Preclinical Development Program, Technology Transfer, Clinical Supply Agreement, or any other activities under this Agreement which the parties may agree will be undertaken by ISIS on an FTE basis, shall be determined by dividing the number of days during any twelve-month period devoted by such employee to the Preclinical Development Program, Technology Transfer, Clinical Supply Agreement, or any other activities under this Agreement which the parties may agree will be undertaken by ISIS on an FTE basis, by the total number of working days during such twelve-month period (including normal vacations, sick days and holidays).

1.13 "Information" shall mean any and all information and data, including without limitation all scientific, preclinical, clinical, regulatory, manufacturing, marketing, financial and commercial information and data, whether communicated in writing or orally or by any other method, which is provided by one party to the other party in connection with this Agreement.

1.14 "ISIS Core Technology" shall mean technology owned or acquired by ISIS as of the Effective Date which claims, covers or relates to linkages and sugar units in an antisense oligonucleotide, wherein such linkages include phosphorothioate linkages and such sugar units include a combination of deoxy sugar units and 2'-O- (2-methoxy- ethyl)- (MOE-) modified sugar units with natural and methyl substituted heterocycle bases ("MOE Gapmer Technology"). ISIS Core Technology also includes technology owned or acquired by ISIS as of the Effective Date which claims, covers or relates to the cellular mechanisms of action by which MOE

*Confidential Treatment Requested 2

Gapmer Technology antisense oligonucleotides exert their effect. ISIS Core Technology does not include any target gene specific technology.

1.15 "ISIS Know-How" shall mean any and all information and materials including without limitation, Compound, Compound Improvements, ISIS Manufacturing Technology, ISIS Core Technology, Manufacturing Technology

Improvements, Core Technology Improvements, processes, methods, protocols, formulas, preclinical, manufacturing and other data, discoveries, inventions, know-how and trade secrets, patentable or otherwise, which during the term of this Agreement (i) are in the possession or control of ISIS or an ISIS Affiliate, (ii) are not generally known and (iii) are necessary or useful to MERCK in the Field including without limitation the development, manufacture, marketing, use or sale of Compound or Product.

1.16 "ISIS Patent Rights" shall mean any and all patents and patent applications in the Territory (which for the purposes of this Agreement shall be deemed to include certificates of invention and applications for certificates of invention) which during the term of this Agreement are owned by ISIS or to which ISIS through license or otherwise acquires rights which (a) claim, cover or relate to Compound and/or Product including without limitation those patents and patent applications which (i) are Compound patents and patent applications listed on Schedule 1.16 (a) (i); or (ii) are ISIS Core Technology patents and patent applications listed on Schedule 1.16 (a) (ii) (to the extent that such ISIS Core Technology patents and patent applications are necessary or useful to Merck in the Field) and patents and patent applications which claim, cover or relate to Core Technology Improvements (to the extent that such Core Technology Improvement patents and patent applications are necessary to Merck to practice effectively in the Field) ; or iii) are ISIS Manufacturing Technology patents and patent applications listed on Schedule 1.16 (a) (iii) (to the extent that such ISIS Manufacturing Technology patents and patent applications are necessary or useful to Merck in the Field) and patents and patent applications which claim, cover or relate to Manufacturing Technology Improvements, to the extent that such Manufacturing Technology Improvement patents and patent applications are necessary or useful to Merck in the Field; or (b) are divisions, continuations, continuations-in-part, reissues, renewals, extensions, supplementary protection certificates, and the like of any of the foregoing patents and patent applications and foreign equivalents thereof.

1.17 "ISIS Manufacturing Technology" shall mean any and all scientific and technical data and information including without limitation formulas, methods, techniques, protocols, and processes owned or acquired by ISIS or an ISIS Affiliate by license or otherwise as of the Effective Date which are necessary or useful to MERCK in the preparation, formulation, analysis, manufacturing or delivery of Compound and/or Product for the purpose of carrying out or implementing the manufacturing process defined generally as the process steps set forth in master batch records for the Compound ISIS 113715[*] including reasonable variants and extensions of process steps thereof.

1.18 "Major Market" shall mean any one of the following countries: United States, Japan, the United Kingdom, France, Germany, Italy or Spain.

1.19 "Manufacturing Technology Improvement" shall mean any and all enhancements, whether or not patentable, in the ISIS Manufacturing Technology arising during the term of this Agreement.

1.20 "Marketing Application" shall mean a New Drug Application (NDA), Worldwide Marketing Authorization (WMA), or Marketing Application Authorization (MAA) or similar application or submission for marketing authorization of a Product filed with a Regulatory Authority including without limitation the FDA.

1.21 "Net Sales" shall mean the gross invoice price of Product sold by MERCK, its Affiliates or sublicensees (which term does not include distributors) to the first independent third party after deducting, if not previously deducted, in the amount invoiced:

(a) trade and quantity discounts other than early pay cash discounts;

(b) returns, rebate, chargebacks and other allowances;

(c) retroactive price reductions;

(d) sales commissions paid to third party distributors;

(e) a fixed amount equal to [*] of the amount invoiced to cover bad debt, sales or excise taxes, early payment cash discounts, transportation and insurance charges, custom duties, and other governmental charges;

(f) the standard inventory cost of devices or delivery systems used for dispensing or administering Product.

With respect to sales of Combination Products, Net Sales shall be calculated on the basis of the invoice price of Product containing the same strength of Compound sold without other active ingredients. In the event that Product is sold only as a Combination Product, Net Sales shall be calculated on the basis of the invoice price of the Combination Product multiplied by a fraction, the numerator of which shall be the inventory cost of Compound in the Product and the denominator of which shall be the inventory cost of all of the active ingredients in the Combination Product. Inventory cost shall be determined in accordance with MERCK's regular accounting methods, consistently applied. The deductions set forth in paragraphs (a) through (f) above will be applied in calculating Net Sales for a Combination Product. In the event that Product is sold only as a Combination Product and either party reasonably believes that the calculation set forth in this Paragraph does not fairly reflect the value of the Product relative to the other active ingredients in the Combination Product, the parties shall negotiate, in good faith, other means of calculating Net Sales with respect to Combination Products.

1.22 "Phase I Clinical Trial" shall mean the first clinical trial in humans in any country including without limitation the first clinical trial in humans that is intended to evaluate the safety, tolerability, pharmacological and/or pharmocokinetic effect of a Compound in human subjects or that would otherwise satisfy the requirements of 21 CFR 312.21(a) or its foreign equivalent.

1.23 "Phase II Clinical Trial" shall mean a human clinical trial in any country that is intended to evaluate the effectiveness of a Compound for a particular indication or indications in human subjects with the disease or indication under study or that would otherwise satisfy the requirements of 21 CFR 312.21(b) or its foreign equivalent. Specifically, a Phase II (a) Clinical Trial shall mean a clinical trial which is the first assessment of efficacy in the target population (and specifically does not include a clinical trial in which the sole endpoints relate to safety or drug interaction), and a Phase II (b) Clinical Trial shall mean a clinical trial which is a definitive dose-ranging study.

1.24 "Phase III Clinical Trial" shall mean a pivotal human clinical trial in any country the results of which could be used to establish safety and efficacy of a Compound as a basis for a Marketing Application or that would otherwise satisfy the requirements of 21 CFR 312.21(c) or its foreign equivalent.

1.25 "Preclinical Development Program" shall mean the preclinical development activities undertaken by MERCK and/or by ISIS, at the direction of MERCK, as set forth in Article II herein and Schedule 2.2 attached hereto as may be amended by the parties from time to time.

1.26 "Product" shall mean preparation(s) in final form for sale by prescription, over-the-counter or any other method for any and all uses in the Field which contain Compound including without limitation any Combination Product.

1.27 "Regulatory Authority" shall mean any applicable government regulatory authority involved in granting approvals for the marketing, and/or pricing of a Product in the Territory, including without limitation, in the United States, the Food and Drug Administration ("FDA"), and any successor government authority having substantially the same function, and foreign equivalents thereof.

1.28 "Technology Transfer" shall have the meaning set forth in Section 7.2.1 herein.

1.29 "Territory" shall mean all of the countries in the world, and their territories and possessions.

1.30 "Valid Patent Claim" shall mean a claim of an issued and unexpired patent included within the ISIS Patent Rights listed on Schedule 1.16 (a) (i) hereto, which has not been revoked or held unenforceable or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or not appealed within the time allowed for appeal, and which has not been disclaimed, denied or admitted to be invalid or unenforceable through reissue or disclaimer or otherwise.

ARTICLE II

PRECLINICAL AND CLINICAL DEVELOPMENT PROGRAM

2.1 GENERAL. ISIS and MERCK shall undertake the Preclinical Development Program activities and MERCK shall undertake the Clinical Development activities upon the terms and conditions set forth in this Agreement.

2.2.1 CONDUCT OF PRECLINICAL DEVELOPMENT PROGRAM. a) The activities to be undertaken by ISIS and MERCK in the course of the Preclinical Development Program shall be at the direction of MERCK, and are set forth in Schedule 2.2. Promptly after the Effective Date, the parties will jointly develop a more detailed Schedule 2.2 relating to the activities, timeline, and budget agreed to in writing by the parties for the Preclinical Development Program, such amended Schedule 2.2 to be attached hereto and made a part of this Agreement. Schedule 2.2 may further be amended from time to time upon prior mutual written agreement of the parties. ISIS and MERCK shall conduct the Preclinical Development Program in a good scientific manner, and in compliance in all material respects with all requirements of applicable laws, rules and regulations to achieve the objectives efficiently and expeditiously. ISIS and MERCK shall proceed diligently with the work set out in Schedule 2.2 using good faith efforts to provide sufficient time, effort, equipment, facilities and skilled personnel to accomplish the objectives set forth in Schedule 2.2.

(b) In no event shall ISIS be entitled to utilize the services of any third party to carry out its obligation under the Preclinical Development Program without the prior written approval of MERCK. ISIS and MERCK hereby acknowledge that MERCK has approved the use by ISIS of third parties listed in the attached Schedule 2.2.1 (b) for the purpose of carrying out certain ISIS' obligations under the Preclinical Development Program as indicated in Schedule 2.2.1 (b). Notwithstanding such approval by MERCK for the use of third parties as set forth herein, ISIS shall remain fully liable for the performance of ISIS' obligations under the Preclinical Development Program. Further, where ISIS is permitted hereunder to utilize third parties to carry out ISIS's obligations under the Preclinical Development Program, ISIS hereby warrants that the terms of any and all agreements with such third parties applicable to activities under the Preclinical Development Program, including without limitation terms relating to confidentiality, record keeping and inspection, inventions and licensing shall be consistent with the terms of this Agreement between ISIS and MERCK. ISIS shall, at MERCK's request, provide MERCK with a copy of any such third party agreements. MERCK shall be entitled (but shall not be obligated), at its discretion, to assume ISIS' rights and responsibilities under such third party agreements applicable to activities under the Preclinical Research Program.

2.2.2 USE OF PRECLINICAL DEVELOPMENT PROGRAM FUNDING. ISIS shall apply the Preclinical Development Program funding it receives from MERCK under this Agreement solely to carry out its obligations under Schedule 2.2 in accordance with the terms of this Agreement and the budget established by the parties.

2.2.3 PRECLINICAL DEVELOPMENT PROGRAM PROJECT LEADERS. Each party shall appoint one (1) project leader who shall be the primary contact between the parties with respect to the Preclinical Development Program and who shall each have appropriate technical credentials, experience and knowledge, and ongoing familiarity with the Preclinical Development Program ("Project Leader"). The Preclinical Development Program shall be conducted under the direction of the Project Leaders. The parties may seek the advice of additional representatives or consultants from time to time, by mutual consent of the parties. In the event that the Project Leaders cannot or do not, after good faith efforts, reach agreement on an issue, the resolution and/or course of conduct shall be determined by MERCK, in its sole discretion, provided that ISIS shall not be required, without its prior written consent, to carry out any additional work not included in Schedule 2.2, as may be amended by the parties.

2.2.4 MEETINGS. The Project Leaders shall meet at least once each month with the location for such meetings alternating between ISIS and MERCK

facilities (or such other locations as is determined by the parties). Alternatively, the Project Leaders may meet by means of teleconference, videoconference or other similar communications equipment. The Project Leaders shall confer regarding the status of the Preclinical Development Program, review relevant data, consider and advise on any technical issues that arise, consider issues of priority, and review and advise on any budgetary and economic matters relating to the Preclinical Development Program.

2.2.5 PRECLINICAL DEVELOPMENT PROGRAM RESULTS AND INVENTIONS. ISIS shall promptly disclose to MERCK the development, making, conception or reduction to practice of all data, information, discoveries, and inventions, patentable or not, arising from the Preclinical Development Program. All such data, information, discoveries, and inventions including without limitations Compound Improvements, patentable or not, arising from the Preclinical Development Program shall be the sole and exclusive property of MERCK, subject to the provisions of Sections 3.4 and 7.2.6 with regard to Core Technology Improvements and Manufacturing Technology Improvements, respectively. MERCK shall promptly disclose to ISIS, prior to filing the relevant patent application, all Core Technology Improvements and Manufacturing Technology Improvements arising from the Preclinical Development Program which shall be subject to the license granted to ISIS hereunder in accordance with the requirements of Sections 3.4 and 7.2.6, respectively, in the event that such Core Technology Improvements or Manufacturing Technology Improvements become patented Core Technology Improvements or patented Manufacturing Technology Improvements.

2.2.6 RECORDS. ISIS shall maintain records, in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes, which shall (a) fully and properly reflect all work done and results achieved in the performance of the Preclinical Development Program, and (b) permit ISIS to provide the CMC Items listed and attached hereto as Schedule 2.2.6 as required by MERCK.

2.2.7 COPIES AND INSPECTION OF RECORDS. MERCK shall have the right, during normal business hours and upon reasonable notice, to inspect and copy all such records of ISIS referred to in Section 2.2.6 including without limitation the CMC Items listed on Schedule 2.2.6 and all preclinical information and data necessary or useful for MERCK for the purposes of filing with Regulatory Authorities hereunder. MERCK shall maintain such records and the information disclosed therein in confidence in accordance with Section 4.1. MERCK shall have the right to arrange for its employees and/or consultants involved in the activities contemplated hereunder to visit the offices and laboratories of ISIS and its third party contractors listed in Schedule 2.2.1 (b) during normal business hours and upon reasonable notice, and to discuss the Preclinical Development Program work and its results in detail with the technical personnel and consultants of ISIS.

2.2.8 QUARTERLY REPORTS. Within thirty (30) days following the end of each Calendar Quarter during the Preclinical Development Program, ISIS shall provide to MERCK, upon MERCK's request, a written progress report which shall describe the work performed to date on the Preclinical Development Program, evaluate the work performed in relation to the goals of the Preclinical Development Program and provide such other information required by the Preclinical Development Program or reasonably requested by

MERCK relating to the progress of the goals or performance of the Preclinical Development Program ("Quarterly Report"). Upon request, ISIS shall provide copies of the records described in Section 2.2.6 above. Further, ISIS shall provide the CMC Items listed in Schedule 2.2.6 in accordance with the timeline to be agreed to by the parties.

2.2.9 COMPLIANCE. ISIS hereby certifies that it has not and will not employ or otherwise use in any capacity any person debarred under Section 21 USC 335(a) in performing any Preclinical Development Program activities.

2.3.1 CLINICAL DEVELOPMENT PROGRAM. MERCK may, at its sole discretion, undertake, and shall solely own the results of, the Clinical Development Program. MERCK shall have the sole responsibility to make any and all regulatory filings for Compound and Product in the Territory as MERCK, in its sole discretion, deems appropriate, and MERCK shall be the sole owner of all regulatory submissions and government approvals therefor. Similarly, MERCK shall have and conduct any and all communications and interactions with regulatory agencies with respect to the Compound and Product, including without limitation

Regulatory Authorities, and other government authorities. ISIS shall cooperate with MERCK in all of these activities whenever and to the extent requested by MERCK, and shall supply MERCK with any and all information necessary or useful to MERCK in preparing and filing regulatory and other government submissions, and in obtaining regulatory and other governmental approvals.

2.3.2 DEVELOPMENT AND COMMERCIALIZATION. MERCK shall use reasonable efforts, consistent with the usual practice followed by MERCK in pursuing the commercialization and marketing of its other similar pharmaceutical products, at its own expense, to develop and commercialize a Product on a commercially reasonable basis in such countries in the Territory where in MERCK's opinion it is commercially viable to do so.

2.3.3 EXCUSED PERFORMANCE. In addition to the provisions of Section 10.1 hereof, the obligations of MERCK with respect to any Product under Section 2.3.2 are expressly conditioned upon the continuing absence of any adverse condition or event relating to the safety or efficacy of the Product, and the obligation of MERCK to develop or market any such Product shall be delayed or suspended so long as in MERCK's opinion any such condition or event exists. All judgments as to safety and efficacy shall be made by MERCK in its sole discretion.

2.3.4 CLINICAL DEVELOPMENT PROGRAM RESULTS AND INVENTIONS. All data, information, inventions and discoveries including without limitation Compound Improvements, patentable or not, resulting from the Clinical Development Program shall be the sole and exclusive property of MERCK, subject to the provisions of Sections 3.4 and 7.2.6 with regard to Core Technology Improvements and Manufacturing Technology Improvements, respectively.

2.4 REPORTING REQUIREMENTS. ISIS and MERCK hereby agree to comply with the reporting requirements set forth in Schedule 2.4 attached hereto, as may be amended in writing by the parties from time to time. In the event of changes to regulatory reporting requirements worldwide, each party agrees to comply with revised notification requirements as reasonably requested in writing by the other party. Notwithstanding the foregoing, MERCK shall have the sole right to report to the Regulatory Authorities any such information relating to the Compound or Product.

ARTICLE III
LICENSE; DISCLOSURE OF INFORMATION

3.1 LICENSE GRANT.

(a) ISIS hereby grants to MERCK an exclusive (exclusive even as to ISIS), sublicensable, royalty-bearing license in the Territory to practice under the ISIS Patent Rights and to utilize the ISIS Know-How to develop, make, have made, use, sell, offer to sell and import Compound and Product in the Field and to otherwise carry out the activities contemplated by this Agreement.

(b) Notwithstanding the foregoing, in the case of ISIS Patent Rights or ISIS Know-How consisting of Core Technology Improvements, MERCK shall be granted an exclusive license to such ISIS Patent Rights and ISIS Know-How in the Field to the extent that such Core Technology Improvements are necessary for MERCK to practice effectively in the Field, and, in the case of such Core Technology Improvements acquired by ISIS from third party(ies) during the term of this Agreement, where such third party rights are sublicensable and MERCK has agreed with ISIS to comply with all obligations relating to such sublicense by ISIS. Further, in the case of ISIS Patent Rights or ISIS Know-How consisting of Manufacturing Technology Improvements acquired by ISIS from third party(ies) during the term of this Agreement, MERCK's shall be granted an exclusive license to such ISIS Patent Rights and ISIS Know-How in the Field where such third party rights are sublicensable and MERCK has agreed with ISIS to comply with all obligations relating to such sublicense by ISIS.

(c) ISIS shall retain the right to practice under the ISIS Patent Rights and to utilize the ISIS Know-How licensed to MERCK hereunder solely as necessary to carry out ISIS' obligations under this Agreement.

(d) For clarification purposes, the parties hereby acknowledge that

MERCK shall have no liability or responsibility for, and ISIS shall be fully liable and responsible for, any payments of any kind whatsoever payable by ISIS to its third party licensors of intellectual property licensed to MERCK by ISIS hereunder.

(e) In addition to the representations and warranties set forth in this Agreement, ISIS hereby agrees, with regard to the ISIS Patent Rights licensed from third parties as set forth in Patent Schedule 1.16(a)(ii), to the following terms and conditions:

(i) ISIS warrants that it will take all actions reasonably necessary to maintain the relevant third party licenses in good standing as to the ISIS Patent Rights sublicensed to MERCK under this Agreement; and

(ii) ISIS shall make all reasonable efforts to notify MERCK as soon as practicable of any notice given or received by ISIS to terminate such third party license(s), and, in the event that such third party license(s) should be terminated for any reason, make all reasonable efforts to obtain for MERCK the right to directly license with the relevant ISIS' third party licensor(s) for the rights sublicensed to MERCK hereunder as of the Effective Date; and,

(iii) In the event that MERCK, due to termination of the relevant license between ISIS and its third party licensor, enter into a direct license with such third party licensor, MERCK shall be entitled to deduct any payments payable by MERCK to such third party licensor from payments due to ISIS under this Agreement.

3.2 NON-EXCLUSIVE LICENSE GRANT. In the event the development, making, having made, use, sale or import by MERCK, its Affiliates and/or sublicensees of Compound (or Product, due to its incorporation of Compound) would infringe during the term of this Agreement a claim of issued letters patent which ISIS owns or has the rights to license and which patents are not covered by the grant in Section 3.1, ISIS hereby grants to MERCK, to the extent ISIS is legally able to do so, a non-exclusive, royalty-free, sublicensable license in the Territory under such issued letters patent solely for MERCK to develop, make, have made, use, sell, offer for sale or import Compound and Product in the Field in the Territory.

3.3 DISCLOSURE OF INFORMATION. During the term of this Agreement, ISIS shall promptly disclose to MERCK in English and in writing on an ongoing basis all ISIS Know-How and other useful information not previously disclosed.

3.4 CORE TECHNOLOGY IMPROVEMENTS. The entire right, title, and interest in and to all Core Technology Improvements, patentable or not, developed or invented solely by employees of ISIS during the term of this Agreement shall be the sole and exclusive property of ISIS, subject to the licenses granted to MERCK under this Agreement. The entire right, title, and interest in and to all Core Technology Improvements, patentable or not, developed or invented solely by employees of MERCK during the term of this Agreement shall be the sole and exclusive property of MERCK, and MERCK hereby grants to ISIS a

worldwide, non-exclusive, sublicensable, royalty-free license to any such patented sole MERCK Core Technology Improvements solely for use outside of the Field. The entire right, title, and interest in and to all Core Technology Improvements, patentable or not, developed or invented jointly by employees of ISIS and MERCK during the term of this Agreement shall be the joint property of ISIS and MERCK, subject to the licenses granted to MERCK under this Agreement. The parties shall promptly disclose to each other the development, making, conception or reduction to practice of all Core Technology Improvements.

3.5 COMPOUND IMPROVEMENTS. The entire right, title, and interest in and to all Compound Improvements, patentable or not, developed or invented solely or jointly by employees of ISIS and/or MERCK during the term of this Agreement shall be the sole and exclusive property of MERCK. ISIS shall promptly disclose to MERCK the development, making, conception or reduction to practice of all Compound Improvements.

3.6 TARGET EXCLUSIVITY. ISIS hereby agrees that, until such time as the approval of the first marketing application for a Compound in a Major Market pursuant to this Agreement, ISIS will work exclusively (even as to ISIS itself) with MERCK with regard to any and all activities for

the research, discovery, development and/or commercialization of antisense compounds and products that target the genetic sequence of PTP-1B.

ARTICLE IV

CONFIDENTIALITY AND PUBLICATION

4.1 NONDISCLOSURE OBLIGATION. All Information disclosed by one party to the other party hereunder shall be maintained in confidence by the receiving party and shall not be disclosed to a non-party or used for any purpose except as set forth herein without the prior written consent of the disclosing party, except to the extent that such Information:

(a) is known by recipient at the time of its receipt, and not through a prior disclosure by the disclosing party, as documented by business records;

(b) is properly in the public domain;

(c) is subsequently disclosed to a receiving party by a third party who may lawfully do so and is not under an obligation of confidentiality to the disclosing party;

(d) is developed by the receiving party independently of Information received from the other party;

(e) is disclosed to governmental or other regulatory agencies by either party in order to obtain patents or by MERCK to gain approval to conduct clinical trials or to market Product, but such disclosure may be only to the extent reasonably necessary to obtain patents or authorizations;

(f) is deemed necessary by MERCK to be disclosed to MERCK sublicensees, agents, consultants, Affiliates and/or other third parties for the development, manufacturing and/or marketing of the Product (or for such parties to determine their interest in performing such activities) in accordance with this Agreement on the condition that such third parties agree to be bound by the confidentiality obligations contained this Agreement, PROVIDED the term of confidentiality for such third parties shall be no less than seven (7) years; or

(g) is required to be disclosed by law or court order, provided that notice is promptly delivered to the other party in order to provide an opportunity to challenge or limit the disclosure obligations.

4.2 PUBLICATION. MERCK shall be entitled to publish on the subject matter of this Agreement, PROVIDED THAT, MERCK shall deliver to ISIS a copy of any proposed publication or an outline of any oral disclosure involving ISIS Manufacturing Technology or ISIS Core Technology at least sixty (60) days prior to submission for publication or presentation, and ISIS shall have the right to request a reasonable delay in such publication or presentation in order to protect patentable information. If ISIS requests a delay, MERCK shall delay submission or presentation for a period of up to thirty (30) days after such planned submission date to enable patent applications to be filed by ISIS in accordance with Article VIII below.

Upon expiration of such thirty-day (30)period, MERCK shall be free to proceed with the publication or presentation. Further, MERCK hereby agrees to provide ISIS, for informational purposes only, with a copy of any proposed MERCK publication involving the Compound once such proposal has been submitted for publication. ISIS shall be permitted to publish on matters relating to the Compound or Product during the term of this Agreement including without limitation any ISIS Know-How only upon the prior written approval of MERCK, which may be given at MERCK's sole discretion. Notwithstanding the foregoing, MERCK acknowledges that, prior to the Effective Date, ISIS and its third party research collaborator(s) have generated data relating to the Compound that ISIS is contractually required to permit such third party research collaborator(s) to publish or present during the term of this Agreement. ISIS agrees to provide MERCK, in advance of the proposed publication or presentation, with copies of any such proposed publication or presentation intended for publication or presentation during the term of this Agreement, and ISIS warrants to MERCK that ISIS

shall not grant such third party collaborators any rights to publish or present such data beyond the rights ISIS is contractually required to grant such third parties as of the Effective Date, and in no case shall ISIS grant such third parties any rights to publish or present data which could negatively impact Compound or Product.

4.3 PUBLICITY. No disclosure of the existence of, or the terms of, this Agreement may be made by either party, and no party shall use the name, trademark, trade name or logo of the other party or its employees in any publicity, news release or disclosure relating to this Agreement, or its subject matter, without the prior express written permission of the other party, except as may be required by law.

ARTICLE V

PAYMENTS; ROYALTIES AND REPORTS

5.1 PROGRAM FUNDING. a) In consideration for ISIS' performance of certain preclinical development activities in connection with the Compound as of [*] such reimbursement to take place within thirty (30) days of the Effective Date and upon receipt of invoice from ISIS. In consideration for ISIS' performance of certain preclinical development activities in connection with the Compound [*] for the performance of such activities, such reimbursement to take place within thirty (30) days of receipt of invoice from ISIS. [*]

b) In consideration for ISIS' performance of its obligations under the Preclinical Development Program, upon the terms and conditions contained herein, MERCK shall pay ISIS for such performance in accordance with the requirements of Schedule 2.2. The FTE rate for Preclinical Development Program work performed directly by ISIS shall be [*] per FTE for any of the following activities undertaken directly by ISIS pursuant to the Preclinical Development Program: drug substance manufacturing; analytical chemistry; process chemistry; formulation; raw material ordering and handling; quality control; or manufacturing technology transfer. The FTE rate for Preclinical Development Program work performed directly by ISIS shall be [*] per FTE for any of the following activities undertaken pursuant to the Preclinical Development Program: toxicology; pharmocokinetics/metabolism; regulatory; clinical development and data management. MERCK shall reimburse ISIS for payments to third parties who have been approved by MERCK to conduct the Preclinical Development Program activities hereunder. ISIS shall invoice MERCK [*] for the amounts payable in accordance with Schedule 2.2. Payments under this Section. 5.1 (b) shall be due thirty (30) days after receipt of each invoice by MERCK. With each [*] invoice after the first [*] invoice provided to MERCK under this Paragraph, ISIS will provide MERCK with copies of third party invoices supporting the invoice amounts charged to MERCK in the prior [*] invoice to MERCK, and ISIS will make any adjustments for overpayment or underpayment therein. If one party is owing the other party as result of such reconciliation process, the owing party will issue a payment to the other party within thirty (30) days. Total payments under this Section shall not exceed [*] without the prior written approval of MERCK for performance of activities under Schedule 2.2.

c) In connection with the Technology Transfer efforts by ISIS hereunder, ISIS shall utilize [*] In consideration for ISIS' performance of its obligations under the Technology Transfer, upon the terms and conditions contained herein, MERCK shall pay ISIS for such performance in accordance with the

requirements of Article VII herein and Schedule 7. 2. ISIS shall invoice MERCK, [*] for all activities performed in accordance with Article VII and the Schedule 7.2. Such invoice shall itemize the activities as set forth in Schedule 7.2. Merck will pay each invoice within thirty (30) days after receipt of invoice and all relevant documentation.

d) In consideration of ISIS' performance of CMC activities in connection with the Compound as set forth in Schedule 2.2.6, and other Compound-specific activities including without limitation specifications development for in-process and release testing of Compound and formulated Compound (including standards, stability programs, and formulation development) and other activities requested by MERCK in support of registration efforts and in

response to regulatory questions and regulatory inspections, where the foregoing activities are required under this Agreement but fall outside ISIS' activities pursuant to the Preclinical Development Program, Technology Transfer and [*] MERCK shall compensate ISIS for such performance at the FTE rate of [*] for any of the following activities undertaken directly by ISIS: analytical chemistry; process chemistry; formulation; drug substance manufacturing, raw material ordering and handling; or manufacturing technology transfer; and, at the FTE rate of [*] for the following activities performed directly by ISIS under this Paragraph (d): toxicology; pharmocokinetics/metabolism; regulatory; clinical development and data management.

Further, where ISIS undertakes other activities such as analytical methods development for raw materials, API, drug product testing and release, and process development in connection with other phosphorothioate 2' deoxyoligonucelotides and MOE Gapmer Technology drugs which support the activities of ISIS with regard to Compound as required pursuant to this Agreement, MERCK will compensate ISIS [*] The FTE rate shall be [*] for any of the following activities undertaken directly by ISIS pursuant to this Section 5.1 (d): analytical chemistry; process chemistry; formulation; drug substance manufacturing, raw material ordering and handling; or manufacturing technology transfer. The FTE rate shall be [*] per FTE for any of the following activities undertaken by ISIS pursuant to this Section 5.1 (d); toxicology; pharmocokinetics/metabolism; regulatory; clinical development and data management.]

5.2 CONSIDERATION FOR RESEARCH FUNDING. [*]

5.3 MILESTONE PAYMENTS.

a) Subject to the terms and conditions of, and during the term of, this Agreement, MERCK shall pay to ISIS [*] each, each such milestone payable only once, upon satisfactory performance of the Preclinical Development Program activities in accordance with the requirements of Schedule 2.2 as Schedule 2.2 may be amended by mutual agreement of the parties. The Preclinical Development milestones set forth in this Section 5.3 (a) shall become payable [*] Notwithstanding the foregoing, in the event that MERCK provides ISIS with a notice of Agreement termination in accordance with the terms of Article 9 herein prior to any such anniversary date, any milestone payment for a milestone achieved during [*] and MERCK shall have no obligation to make any such milestone payment to ISIS.

b) Subject to the terms and conditions of, and during the term of, this Agreement, MERCK shall pay to ISIS the following Development milestone payments with respect to each Compound in development for diabetes, each milestone payment to be made no more than once with respect to such Compound:

(i) [*]

(ii) [*]

(iii) [*]

(iv) [*]

(v) [*]

c) Subject to the terms and conditions of, and during the term of, this Agreement, MERCK shall pay to ISIS the following Development milestone payments with respect to each Compound for obesity, each milestone payment to be made no more than once with respect to each such Compound:

(i) [*]

(ii) [*]

(iii) [*]

MERCK shall notify ISIS in writing within thirty (30) days upon the achievement of each Development milestone set forth in Sections 5.3 (b) and (c), such notice to be accompanied by payment of the appropriate

milestone payment. The milestone payment shall be payable only upon the initial achievement of such milestone and no amounts shall be due hereunder for subsequent or repeated achievement of such milestone. Should the development of a Compound for an indication be discontinued, any Development milestone payment(s) previously paid hereunder for a Compound for such indication shall not be payable by MERCK for any other Compound developed by MERCK hereunder for the same indication. In the event that MERCK achieves any Developmental Milestone set forth in Sections 5.3 (b) or (c) without having achieved prior Developmental Milestone(s) set forth in the relevant Section for the same indication, Merck shall be obligated to pay all such prior Developmental Milestones not previously paid, upon achievement of such subsequent Developmental Milestone for the same indication.

ROYALTIES.

5.4.1 ROYALTIES PAYABLE BY MERCK. Subject to the terms and conditions of, and during the term of, this Agreement, MERCK shall pay to ISIS royalties in an amount equal to:

(a) [*] of the aggregate annual worldwide Net Sales of each Product by MERCK, its Affiliates or sublicensees where such aggregate annual worldwide Net Sales are less than [*] as set forth below, provided the sale of the Product would, but for the license hereunder, infringe a Valid Patent Claim in the country of sale, or

(b) [*] of the aggregate annual worldwide Net Sales of each Product by MERCK, its Affiliates or sublicensees where such aggregate annual worldwide Net Sales are equal to or greater than [*] as set forth below, provided the sale of the Product would, but for the license hereunder, infringe a Valid Patent Claim in the country of sale, or

(c) For Net Sales of Products by MERCK, its Affiliates or sublicensees other than those covered by Subsection 5.4.1. (a) or 5.4.1 (b), the royalty rate shall be [*] but in no event shall such royalty pursuant to this Subsection 5.4.1 (c) [*]

Royalties on each Product at the rate set forth above shall be effective as of the date of First Commercial Sale of Product in a country and shall continue until either (i) the expiration of the last applicable patent on such Product in such country in the case of sales under Subsection 5.4.1(a) and (b), [*] in the case of sales of Product under Subsection 5.4.1(c) above. Notwithstanding the foregoing, under Subsection (ii) of this Paragraph, [*] However, in no event shall such pass through royalties be payable by Merck after such ISIS' royalty obligations to such third party licensor(s) have terminated. Royalty payments pursuant to Subsection 5.4.1 are subject to the following conditions:

(x) that only one royalty shall be due with respect to the same unit of Product;

(y) that no royalties shall be due upon the sale or other transfer among MERCK, its Affiliates or sublicensees, but in such cases the royalty shall be due and calculated upon MERCK's or its Affiliate's or its sublicensee's Net Sales to the first independent third party; and (z) no royalties shall accrue on the disposition of Product in reasonable quantities by MERCK, Affiliates or its sublicenses as samples (promotion or otherwise) or as donations (for example, to non-profit institutions or government agencies for a non-commercial purpose).

In the event that MERCK sells Product for end use or consumption prior to receiving all required approvals from the governing Regulatory Authority of the country of sale, including without limitation for compassionate use purposes, the first such sale for end use or consumption of such Product in such country shall be deemed a First Commercial Sale hereunder for the purpose of establishing the effective date for the initiation of payment of royalties in such country as set forth above, however, [*]set forth in Section (ii) above shall commence upon the date of First Commercial Sale after all required approvals have been granted, as set forth in Section 1.11 of this Agreement.

5.4.2 ROYALTY PAYABLE UNDER MANAGED PHARMACEUTICAL CONTRACT. It is understood by the parties that MERCK may sell Product to an independent third party (such as a retailer or wholesaler) and may subsequently perform services relating to Product and other products under a managed pharmaceutical benefits contract or other similar contract. In such cases, it is agreed by the parties that Net Sales shall be based on the invoice price to such independent retailer or wholesaler, as set forth in Section 1.21, notwithstanding that MERCK or its Affiliates may receive compensation arising from the performance of such services.

5.4.3 CHANGE IN SALES PRACTICES. The parties acknowledge that during the term of this Agreement, MERCK's sales practices for the marketing and distribution of Product may change to the extent to which the calculation of the payment for royalties on Net Sales may become impractical or even impossible. In such event the parties agree to meet and discuss in good faith new ways of compensating ISIS to the extent currently contemplated under Section 5.4.1.

5.4.4 ROYALTIES FOR BULK FORMULATED COMPOUND. In those cases where MERCK sells bulk formulated Compound, rather than Product in packaged form, to an independent third party, the royalty obligations of this Article V shall be applicable to the bulk formulated Compound.

5.4.5 COMPULSORY LICENSES. If a compulsory license is granted to a third party with respect to Product in any country in the Territory with a royalty rate lower than the royalty rate provided by Section 5.4.1., then the royalty rate to be paid by MERCK on Net Sales in that country under Section 5.4.1 shall be reduced to the rate paid by the compulsory licensee.

5.4.6 THIRD PARTY LICENSES. In the event that one or more patent licenses from other third parties are required by MERCK, its Affiliates and sublicensees to practice the ISIS Patent Rights or to utilize the ISIS Know-How in order to develop, make, have made, use, import, offer to sell or sell Compound (or Product, due to the incorporation of Compound) (hereinafter "Third Party Patent Licenses"). [*] In the event that MERCK acquires patent license(s) from third parties pursuant to this Subsection 5.4.6, and such license(s) are both sublicensable, and useful outside the Field, MERCK hereby grants ISIS a non-exclusive, royalty-free sublicense under such patent license(s) solely for use outside the Field, such sublicense to be subject to the obligations of such third party license(s) to MERCK.]

5.5 REPORTS; PAYMENT OF ROYALTY. During the term of the Agreement following the First Commercial Sale of a Product, MERCK shall furnish to ISIS a [*] written report for the [*] showing the Net Sales of all Products subject to royalty payments sold by MERCK, its Affiliates and its sublicensees in the Territory during the reporting period and the royalties payable under this Agreement. MERCK shall provide ISIS, for ISIS' convenience, [*] Reports of actual information as required in this Subsection 5.5 above shall be due on the [*] following the close of each [*] Royalties shown to have accrued by each such [*] royalty report shall be due and payable on the date such royalty report is due [*] following the close of each [*] MERCK shall keep complete and accurate records in sufficient detail to enable the royalties payable hereunder to be determined.

5.6 AUDITS.

(a) Upon the written request of ISIS and not more than once in each Calendar Year, MERCK shall permit an independent certified public accounting firm of nationally recognized standing selected by ISIS and reasonably acceptable to MERCK, at ISIS's expense, to have access during normal business hours to such of the records of MERCK as may be necessary to verify the accuracy of the royalty reports hereunder for any year ending not more than twenty-four (24) months prior to the date of such request. Such records shall consist of the Net Sales figure for each Product, and the Coefficient for each Product, as reported on a quarterly basis within MERCK's internal worldwide accounting system. The accounting firm shall disclose to ISIS only whether the royalty reports are correct or incorrect and the specific details concerning any discrepancies. No other information shall be provided to ISIS.

(b) If such accounting firm correctly concludes that additional royalties were owed during such period, MERCK shall pay the additional royalties within thirty (30) days of the date ISIS delivers to MERCK such accounting firm's written report so correctly concluding. The fees charged by such accounting firm shall be paid by ISIS [*]

(c) MERCK shall include in each sublicense granted by it pursuant to this Agreement a provision requiring the sublicensee to make reports to MERCK, to keep and maintain records of sales made pursuant to such sublicense and to grant access to such records by ISIS's independent accountant to the same extent required of MERCK under this Agreement.

(d) Upon the expiration of [*] months following the end of any year, the calculation of royalties payable with respect to such year shall be binding and conclusive upon ISIS, and MERCK and its sublicensees shall be released from any liability or accountability with respect to royalties for such year.

(e) ISIS shall treat all financial information subject to review under this Section 5.6 or under any sublicense agreement as MERCK Information in accordance with the confidentiality and non-use provisions of this Agreement, and shall cause its accounting firm to enter into an acceptable confidentiality agreement with MERCK and its sublicensees obligating such accounting firms to retain all such financial information in confidence pursuant to such confidentiality and non-use provisions.

5.7 PAYMENT EXCHANGE RATE. All payments to be made by MERCK to ISIS under this Agreement shall be made in United States dollars and may be paid by check made to the order of ISIS or bank wire transfer in immediately available funds to such bank account in the United States designated in writing by ISIS from time to time. In the case of sales invoiced in a foreign currency, exchange conversion of such sales into United States dollars shall be made on a monthly basis and shall be made at the rate of exchange utilized by MERCK in its worldwide accounting system prevailing on the third to the last business day preceding the month in which sales are recorded by MERCK.

5.8 INCOME TAX WITHHOLDING. If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in this Article V, MERCK shall make such withholding payments as required and subtract such withholding payments from the payments set forth in this Article V. MERCK shall submit appropriate proof of payment of the withholding taxes to ISIS within a reasonable period of time.

ARTICLE VI

REPRESENTATIONS, WARRANTIES AND INDEMNITY

6.1 REPRESENTATION AND WARRANTY. ISIS represents and warrants to MERCK that, as of the date of this Agreement:

(a) to the best of ISIS' knowledge, the ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology and ISIS Know-How are subsisting and are not invalid or unenforceable, in whole or in part;

(b) it has the full right, power and authority to enter into this Agreement, to perform the Preclinical Development Program and Technology Transfer, and to grant the licenses granted under Article III hereof;

(c) it has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology or ISIS Know-How in a manner that would interfere with ISIS' ability to grant the licenses granted to MERCK under this Agreement;

(d) it is the sole and exclusive owner of the Compound and the patent applications claiming Compound set forth in Schedule 1.16 (a) (i) herein, and has the rights in and to the ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology and ISIS Know-How necessary and sufficient to grant to MERCK the rights licensed to MERCK under this Agreement all of which are free and clear of any liens, charges and encumbrances, and no

other person, corporate or other private entity, or governmental entity or subdivision thereof, has or shall have any claim of ownership with respect to the ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology and ISIS Know-How licensed to MERCK under this Agreement that would interfere with the licenses granted to MERCK under this Agreement, whatsoever;

(e) to the best of ISIS' knowledge, the licensed ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology and ISIS Know-How and the development, manufacture, use, sale and import of Compound and Product do not interfere with or infringe any intellectual property rights owned or possessed by any third party;

(f) there are no claims, judgments or settlements against or owed by ISIS or pending or threatened claims or litigation relating to the ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology or ISIS Know-How; and

(g) ISIS has disclosed to MERCK all reasonably relevant information regarding ISIS Patent Rights, ISIS Manufacturing Technology, ISIS Core Technology and ISIS Know-How licensed under this Agreement, including all patent opinions obtained by ISIS related thereto.

6.2 INDEMNITY. a) ISIS shall indemnify, defend and hold MERCK and its Affiliates, and their respective directors, officers, employees and agents harmless against any and all losses, costs, liabilities and expenses (including reasonable attorneys' fees), actions, suits, claims, demands and prosecution that may be brought or instituted to the extent based upon or arising out of i) the negligence or willful misconduct of ISIS under this Agreement, or ii) the material breach by ISIS of any warranty, representation or obligation of ISIS under this Agreement.

b) MERCK shall indemnify, defend and hold ISIS and its Affiliates, and their respective directors, officers, employees and agents harmless against any and all losses, costs, liabilities and expenses (including reasonable attorneys' fees), actions, suits, claims, demands and prosecution that may be brought or instituted to the extent based upon or arising out of i) the negligence or willful misconduct of MERCK under this Agreement, ii) the material breach by MERCK of any warranty, representation or obligation of MERCK under this Agreement, or iii) the use, manufacture or sale by MERCK of Compound or Product.

ARTICLE VII

CLINICAL SUPPLY AND TECHNOLOGY TRANSFER

7.1 CLINICAL SUPPLY. ISIS hereby agrees to supply MERCK with its worldwide requirements for API, Intermediate Compound, Placebo and Clinical Product (as the foregoing terms are defined in the Clinical Supply Agreement) in accordance with the terms of the Clinical Supply Agreement. In the event that ISIS does not have sufficient manufacturing capacity to meet MERCK's requirements in accordance with the terms of the Clinical Supply Agreement, ISIS may use a third party toll manufacturer to manufacture all or part of MERCK's requirements, upon the prior written approval of MERCK. MERCK shall supply its own requirements for Compound and Products for development and commercialization on a worldwide

basis upon completion of the Technology Transfer in accordance with the terms of this Agreement. Concurrently with the execution of this Agreement, the parties shall execute the Clinical Supply Agreement attached hereto as Schedule 1.5.

7.2.1 TECHNOLOGY TRANSFER. Commencing with the Effective Date and for a time period thereafter to be determined by the Committee (the "Technology Transfer Term") and in accordance with the terms and conditions set forth in this Agreement, ISIS promptly shall (a) disclose to and transfer to MERCK all of the ISIS Know-How and ISIS Technology including the items listed in Schedule 7.2 and those items more fully detailed in the Technology Transfer Work Plan to be agreed to by the parties within thirty (30) days after the Effective Date and (b) provide to MERCK the training and support described in Schedule 7.2 and the Technology Transfer Work Plan and elsewhere in this Agreement to enable MERCK to efficiently and economically optimize use of the ISIS Know-How, ISIS Technology and ISIS Patent Rights, in the

formulation, development, registration, manufacture, marketing and sale of Compound and Product in the Field (the "Technology Transfer"). ISIS shall perform the Technology Transfer in accordance with the Procedures established by the Committee in accordance with Section 7.2.3. The parties shall cooperate so that the Technology Transfer may be completed as expeditiously as possible.

7.2.2 TECHNOLOGY TRANSFER COMMITTEE. The Technology Transfer shall be coordinated and implemented under the supervision of a joint committee (the "Committee") comprised of an agreed number of employees appointed by the parties having appropriate technical credentials, experience and knowledge and co-chaired by an employee of each party. The advice of additional employees or consultants of either party may by mutual consent of the parties be obtained. Decisions of the Committee shall be made by unanimous decision of the two-co-chairs; provided however, in the event that the co-chairs do not, after good faith efforts, reach agreement on an issue, the resolution and/or course of conduct in issue shall be determined in good faith by the Executive Vice President, Science and Technology, and President of MERCK Research Laboratories, and the Executive Vice President of ISIS; provided, however, in the event that they do not, after good faith efforts, reach agreement on an issue, the issue shall be submitted to arbitration pursuant to Section 10.6. Throughout the entire Technology Transfer Term, the Committee shall meet at least once each month in person or by teleconference, videoconference or by other mutually acceptable means. The Committee shall establish the Procedures, confer regarding the status of the Technology Transfer and compliance with the Procedures, review relevant data and results achieved, consider and advise on any technical issues that arise, consider issues of priority, and review and advise on any matters relating to the Technology Transfer referred to the Committee.

7.2.3 PROCEDURES FOR TECHNOLOGY TRANSFER. Promptly after the Effective Date, the Committee shall commence to monitor compliance with the procedures set forth in Schedule 7.2 and the Technology Transfer Work Plan which shall detail the procedures for the prompt and efficient Technology Transfer, and shall describe the events necessary to accomplish the Technology Transfer and detail the training and support to be provided by ISIS during the Technology Transfer (the "Procedures"). The Procedures shall be designed to ensure, and shall be refined by the Committee as necessary to ensure, MERCK's optimal use of the ISIS Know-How, ISIS Technology and ISIS Patent Rights in developing, manufacturing and commercializing Compound and Product, all in accordance with the terms of this Agreement.

7.2.4 TRAINING AND SUPPORT. The training and support to be provided by ISIS to MERCK throughout the Technology Transfer Term shall include without limitation training and support in a mutually acceptable MERCK facility in all of the methods necessary to practice the ISIS Know-How, ISIS Technology and ISIS Patent Rights in the development, manufacturing and commercialization of Compound and Product, and this shall include without limitation (a) demonstration and training during the installation, operational and performance qualifications of the technology, (b) technical support for the operational startup of manufacturing equipment, and (c) demonstration of the manufacturing processes. In addition, a reasonable number of employees of MERCK and its Affiliates shall be entitled to visit ISIS facilities including without limitation pilot and commercial scale facilities and testing laboratories to observe relevant processes in operation. Moreover, ISIS shall provide technical consultation on an as-needed basis following NDA approval of Product for a time period to be established by the Committee. ISIS also shall be available, if requested, for consultation during any regulatory inspection or to assist in responding to regulatory questions that may occur during Product registration activities.

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

ISIS.

7.2.6 MANUFACTURING TECHNOLOGY IMPROVEMENTS. The entire right, title, and interest in and to all Manufacturing Technology Improvements, patentable or not, developed or invented solely by employees of ISIS during the term of this Agreement shall be the sole and exclusive property of ISIS, subject to the licenses granted to MERCK under this Agreement. The entire right, title, and interest in and to all Manufacturing Technology Improvements, patentable or not, developed or invented solely by employees of MERCK during the term of this Agreement shall be the sole and exclusive property of MERCK, and MERCK hereby grants to ISIS a worldwide, non-exclusive, sublicensable, royalty-free license to any such patented sole MERCK Manufacturing Technology Improvements solely for use outside of the Field. The entire right, title, and interest in and to all Manufacturing Technology Improvements, patentable or not, developed or invented jointly by employees of ISIS and MERCK during the term of this Agreement shall be the joint property of ISIS and MERCK, subject to the licenses granted to MERCK under this Agreement. The parties shall promptly disclose to each other the development, making, conception or reduction to practice of all Manufacturing Technology Improvements.

ARTICLE VIII

PATENT PROVISIONS

8.1 FILING, PROSECUTION AND MAINTENANCE OF PATENTS. ISIS and MERCK hereby agree that, during the term of this Agreement, the ISIS Patent Rights which claim, cover or relate to the Compound in the Territory shall, at MERCK's expense, be filed, prosecuted and maintained by independent patent legal counsel chosen by MERCK and reasonably acceptable to ISIS. Such independent counsel shall keep ISIS and MERCK advised of the status of the actual and prospective patent filings and upon the request of the party(ies), shall provide advance copies of any papers related to the filing, prosecution and maintenance. The parties shall consult as to patent filings by such independent counsel which shall be subject to the prior mutual agreement of the parties. ISIS agrees to file, prosecute and maintain in the Territory the ISIS Patent Rights which claim, cover or relate to Core Technology, Core Technology Improvements, Manufacturing Technology or Manufacturing Technology Improvements owned in whole or in part by ISIS and licensed to MERCK under this Agreement. ISIS shall keep MERCK advised of the status of the actual and prospective patent filings on a semi-annual basis and upon the request of MERCK, provide copies of any papers related to the filing, prosecution and maintenance of such patent filings. MERCK shall have the exclusive right during the term of this Agreement to file, prosecute and maintain, in the Territory, patent applications that claim, cover or relate to Compound Improvements. With respect to all filings hereunder, the filing party shall be responsible for payment for all costs and expenses related to such filings.

8.2 ISIS PATENT RIGHTS PATENT SCHEDULES. ISIS hereby agrees to provide MERCK with updated patent schedules in a timeframe agreed to by the parties.

8.3 INTERFERENCE, OPPOSITION, REEXAMINATION AND REISSUE. Either party shall, within ten (10) days of learning of such event, inform the other party of any request for, or filing or declaration of, any interference, opposition, or reexamination relating to ISIS Patent Rights in the Field. MERCK and ISIS shall thereafter consult and cooperate fully to determine a course of action with respect to any such proceeding subject to the following:

(a) Any interference, opposition, reissue, or reexamination proceeding relating to ISIS Patent Rights which claim, cover or relate to Compound in the Territory shall be conducted at MERCK's expense by independent patent legal counsel chosen by MERCK and reasonably acceptable to

ISIS. MERCK and ISIS will cooperate fully and will provide each other and the independent patent legal counsel with any information or assistance that any party may reasonably request. Outside patent legal counsel shall keep MERCK and ISIS informed of developments in any such action or proceeding. Decisions on whether to initiate such a proceeding and the course of action in such proceeding, including settlement negotiations and terms, shall be made by mutual agreement of ISIS and MERCK.

(b) Any interference, opposition, reissue, or reexamination proceeding relating to ISIS Patent Rights which claim, cover or relate to the Core Technology, Core Technology Improvements, Manufacturing Technology or Manufacturing Technology Improvements in the Territory, shall be conducted by ISIS at ISIS' expense. To the extent that such interference, opposition, reissue, or reexamination proceeding materially impacts MERCK's rights within the Field, MERCK and ISIS will cooperate fully and will provide each other with any information or assistance that either may reasonably request. ISIS shall keep MERCK informed of developments in any such action or proceeding, including, to the extent permissible, the status of any settlement negotiations and the terms of any offer related thereto, except that ISIS must obtain MERCK's consent to any settlement terms which affect MERCK's freedom to operate in the Field under the licenses granted to MERCK under this Agreement.

8.4 ENFORCEMENT AND DEFENSE.

(a) ISIS shall give MERCK notice of (i) any infringement of ISIS Patent Rights in the Field, or (ii) any misappropriation or misuse of ISIS Know-How in the Field, that may come to ISIS's attention. MERCK and ISIS shall thereafter consult and cooperate fully to determine a course of action, including without limitation the commencement of legal action by either or both MERCK and ISIS, to terminate any infringement of ISIS Patent Rights or any misappropriation or misuse of ISIS Know-How in the Field. However, ISIS, upon notice to MERCK, shall have the first right to initiate and prosecute such legal action at its own expense and in the name of ISIS and MERCK, or to control the defense of any declaratory judgment action relating to ISIS Patent Rights or ISIS Know-How in the Field. ISIS shall promptly inform MERCK if it elects not to exercise such first right and MERCK shall thereafter have the right to either initiate and prosecute such action or to control the defense of such declaratory judgment action in the name of MERCK and, if necessary, ISIS.

(b) In the event that ISIS elects not to initiate and prosecute an action as provided in paragraph (a), and MERCK elects to do so, the costs of any agreed-upon course of action to terminate infringement of ISIS Patent Rights or misappropriation or misuse of ISIS Know-How, including the costs of any legal action commenced or the defense of any declaratory judgment, shall be shared equally by ISIS and MERCK, except that the cost of any such action related solely to the Compound shall be borne by MERCK.

(c) For any action to terminate any infringement of ISIS Patent Rights or any misappropriation or misuse of ISIS Know-How, in the event that MERCK is unable to initiate or prosecute such action solely in its own name, ISIS will join such action voluntarily and will execute and cause its Affiliates to execute all documents necessary for MERCK to initiate litigation to prosecute and maintain such action. In connection with any action, MERCK and ISIS will cooperate fully and will provide each other with any information or assistance that either may reasonably request. Each party shall keep the other informed of developments in any action or proceeding, including, to the extent permissible by law, the status of any settlement negotiations and the terms of any offer related thereto.

(d) Any recovery obtained by either or both MERCK and ISIS in connection with or as a result of any action contemplated by this section, whether by settlement or otherwise, shall be shared in order as follows:

(i) the party which initiated and prosecuted the action shall recoup all of its costs and expenses incurred in connection with the action;

(ii) the other party shall then, to the extent possible, recover its costs and expenses incurred in connection with the action; and

(iii) the amount of any recovery remaining shall then be allocated between the parties on a PRO RATA basis under which ISIS shall receive a proportion based on the royalties it lost and MERCK shall receive a proportion based on its lost profits.

(e) ISIS shall inform MERCK of any certification regarding any ISIS Patent Rights it has received pursuant to either 21 U.S.C. Sections 355(b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) or under Canada's Patented medicines (Notice of Compliance) Regulations Article 5 and shall provide MERCK with a copy of such certification within five (5) days of receipt. ISIS's and MERCK's rights with respect to the initiation and prosecution of any legal action as a result of such certification or any recovery obtained as a result of such legal action shall be as defined in paragraphs (a)-(d) hereof; provided, however, that ISIS shall exercise its first right to initiate and prosecute any action and shall inform MERCK of such decision within ten (10) days of receipt of the certification, after which time MERCK shall have the right to initiate and prosecute such action.

8.5 CERTIFICATION UNDER DRUG PRICE COMPETITION AND PATENT RESTORATION ACT. ISIS and MERCK each shall immediately give notice to the other of any certification of which they become aware filed under the United States "Drug Price Competition and Patent Term Restoration Act of 1984" claiming that ISIS Patent Rights covering Compound or Product are invalid or that infringement will not arise from the manufacture, use or sale of Compound(s) or Product(s) by a third party. If ISIS or MERCK (depending on which party is defending the ISIS Patent Rights) decides not to bring infringement proceedings against the entity making such a certification, such party shall give notice to the other party of its decision not to bring suit within twenty-one (21) days after receipt of notice of such certification. The party receiving such notice may then, but is not required to, bring suit against the party that filed the certification. Any suit by MERCK or ISIS shall either be in the name of MERCK or in the name of ISIS, or jointly by MERCK and ISIS. For this purpose, the party not bringing suit shall execute such legal papers necessary for the prosecution of such suit as may be reasonably requested by the party bringing suit.

8.6 ABANDONMENT. ISIS shall promptly give notice to MERCK of the grant, lapse, revocation, surrender, invalidation or abandonment of any ISIS Patent Rights licensed to MERCK for which ISIS is responsible for the filing, prosecution and maintenance.

8.7 PATENT TERM RESTORATION. The parties hereto shall cooperate with each other in obtaining patent term restoration or supplemental protection certificates or their equivalents in any country in the Territory where applicable to ISIS Patent Rights. In the event that elections with respect to obtaining such patent term restoration are to be made, MERCK shall have the right to make the election and ISIS agrees to abide by such election.

ARTICLE IX

TERM AND TERMINATION

9.1 TERM AND EXPIRATION. This Agreement shall be effective as of the Effective Date and unless terminated earlier pursuant to Sections 9.2 or 9.3 below, the term of this Agreement shall continue in effect until expiration of all royalty obligations hereunder. Upon expiration of this Agreement due to expiration of all royalty obligations hereunder, MERCK's licenses pursuant to Section 3.1 and 3.2 shall become fully paid-up, perpetual licenses.

9.2 TERMINATION BY MERCK. a) Notwithstanding anything contained herein to the contrary, MERCK shall have the right to terminate this Agreement at any time in its sole discretion a) during the Preclinical Development Program by giving thirty (30) days advanced written notice to ISIS, and b) thereafter by giving ninety (90) days advance written notice to ISIS. b) In the event of such termination by MERCK, the rights and obligations hereunder, including any payment obligations not due and owing as of the termination date, shall terminate, subject to the provisions of Section 9.4 herein, provided that MERCK shall be obligated to pay all non-cancelable commitments to undertake Preclinical Development Program studies in accordance with Schedule 2.2 and the terms of this Agreement, and all other non-cancelable Agreement commitments undertaken by ISIS in accordance with the terms of this Agreement, where such non-cancelable commitments exist as of the date of notice of termination is provided by MERCK. c) In the

event that MERCK terminates this Agreement pursuant to this Section 9.2 after the commencement of Clinical Development studies by MERCK for reasons other than safety, and ISIS notifies MERCK within ninety (90) days after such termination that ISIS wishes to commercialize the Compound, the parties hereof agree to enter into negotiations for a

commercially reasonable arrangement to permit ISIS to undertake development and commercialization of the Compound utilizing summaries of Clinical Development Program data developed by MERCK under this Agreement. [*]

9.3 TERMINATION.

9.3.1 TERMINATION FOR CAUSE. This Agreement may be terminated by notice by either party at any time during the term of this Agreement:

(a) if the other party is in breach of its material obligations hereunder by causes and reasons within its control and has not cured such breach within ninety (90) days after notice requesting cure of the breach; providing, however, that in the event of a good faith dispute with respect to the existence of a material breach, the ninety (90) day cure period shall be stayed until such time as the dispute is resolved pursuant to Subsection 10.6 hereof; and

(b) upon the filing or institution of bankruptcy, reorganization, liquidation or receivership proceedings, or upon an assignment of a substantial portion of the assets for the benefit of creditors by the other party; PROVIDED, HOWEVER, in the case of any involuntary bankruptcy proceeding such right to terminate shall only become effective if the party consents to the involuntary bankruptcy or such proceeding is not dismissed within ninety (90) days after the filing thereof.

9.3.2 EFFECT OF TERMINATION FOR CAUSE ON LICENSE.

(a) In the event MERCK terminates this Agreement under Section 9.3.1(a), MERCK's licenses pursuant to Sections 3.1 and 3.2 shall become perpetual licenses. It is understood that in the event MERCK contends it suffers damages as a result of the breach, MERCK may place a portion of the payments to be made by MERCK pursuant to Article 5 that would reasonably cover MERCK's alleged damages into an interest-bearing escrow account pending resolution of any dispute between the parties relating to the material breach or termination of the agreement, including a dispute over damages, pursuant to paragraph 10.6. In the event that ISIS terminates this Agreement under Section 9.3.1(a), MERCK's licenses pursuant to Sections 3.1 and 3.2 shall terminate as of such termination date.

(b) In the event this Agreement is terminated by MERCK under Section 9.3.1(b) or due to the rejection of this Agreement by or on behalf of ISIS under Section 365 of the United States Bankruptcy Code (the "Code"), all licenses and rights to licenses granted under or pursuant to this Agreement by ISIS to MERCK are, and shall otherwise be deemed to be, for purposes of Section 365(n) of the Code, licenses of rights to "intellectual property" as defined under Section 101(35A) of the Code. The parties agree that MERCK, as a licensee of such rights under this Agreement, shall retain and may fully exercise all of its rights and elections under the Code, and that upon commencement of a bankruptcy proceeding by or against ISIS under the Code, MERCK shall be entitled to a complete duplicate of or complete access to (as MERCK deems appropriate), any such intellectual property and all embodiments of such intellectual property. Such intellectual property and all embodiments thereof shall be promptly delivered to MERCK (i) upon any such commencement of a bankruptcy proceeding upon written request therefore by MERCK, unless ISIS elects to continue to perform all of its obligations under this Agreement or (ii) if not delivered under (i) above, upon the rejection of this Agreement by or on behalf of ISIS upon written request therefore by MERCK. Where MERCK does retain and is able to fully exercise all licenses and rights to licenses granted under this Agreement, MERCK's payment obligations to ISIS for milestones and royalties in accordance with Section 5.3 and/or Section 5.4 of this Agreement in connection with such exercise by MERCK of MERCK's licenses hereunder shall continue in effect.

The foregoing is without prejudice to any rights MERCK may have arising under the Code or other applicable law.

9.4 EFFECT OF EXPIRATION OR TERMINATION. (a) Expiration or termination of the Agreement shall not relieve the parties of any obligation accruing

prior to such expiration or termination, Sections 2.2.5, 2.2.6, 2.2.7, 2.3.4, 3.1 (d), 3.4, 3.5, 7.2.5, 7.2.6, 9.1, 9.2, 9.3.2, 9.4, 10.4, 10.5 and 10.6 shall survive expiration or termination of the Agreement, the provisions of Article IV shall survive the termination or expiration of the Agreement and shall continue in effect for ten (10) years thereafter, and the provisions of 2.4 and Schedule 2.4 shall continue in effect in accordance with the application timetable set forth therein. Any expiration or early termination of this Agreement shall be without prejudice to the rights of either party against the other accrued or accruing under this Agreement prior to termination, including the obligation to pay royalties for Product or Compound sold prior to such termination.

(b) Upon any termination of this Agreement by MERCK pursuant to Subsection 9.2, or by ISIS pursuant to Subsection 9.3.1, MERCK shall be entitled, during the twelve (12) months following the termination date, to finish any work-in-progress and to sell any inventory of Compound and Product which remains on hand.

ARTICLE X

MISCELLANEOUS

10.1 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 when such failure or delay is caused by or results from causes beyond the reasonable control of the affected party including without limitation embargoes, war, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, or acts of God. The affected party shall notify the other party of such force majeure circumstances as soon as reasonably practical and shall make every reasonable effort to mitigate the effects of such force majeure circumstances.

10.2 ASSIGNMENT. This Agreement shall inure to the benefit and be binding upon each party, its successors and assigns. The Agreement may not be assigned or otherwise transferred, nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred by either party without the prior written consent of the other party; PROVIDED, HOWEVER, that MERCK may, without such consent, assign the Agreement and its rights and obligations hereunder to an Affiliate or in connection with the transfer or sale of all or substantially all of its assets related to the Product or the business, or in the event of its merger or consolidation or change in control or similar transaction, and PROVIDED, HOWEVER, that ISIS may, without such consent, assign the Agreement and its rights and obligations hereunder in connection with the transfer or sale of all or substantially all of its assets, or in the event of its merger or consolidation or change in control or similar transaction. Any permitted assignee shall assume all obligations of its assignor under the Agreement. Any attempted assignment not in accordance with this Section 10.2 shall be void.

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

10.4 NOTICES. All notices which are required or permitted hereunder shall be in writing and sufficient if delivered personally, sent by facsimile (and promptly confirmed by personal delivery, registered or

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

if to ISIS, to: ISIS Pharmaceuticals, Inc.
Carlsbad Research Center

2292 Faraday Avenue
Carlsbad, CA 92008
Attention: Executive Vice President
Fax No.: (760) 931-9639

with a copy to: Attention: General Counsel
Fax No.: (760) 603-3820

if to MERCK, to: Merck & Co., Inc.
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100
Attention: Vice President,
Corporate Development and Licensing

with a copy to: Attention: Office of the Secretary

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

10.5 APPLICABLE LAW. The Agreement shall be governed by and construed in accordance with the laws of the State of New Jersey without reference to any rules of conflict of laws or renvoi.

10.6 DISPUTE RESOLUTION. The parties shall negotiate in good faith and use reasonable efforts to settle any dispute, controversy or claim arising from or related to this Agreement or the breach thereof. If the parties do not fully settle, and a party wishes to pursue the matter, each such dispute, controversy or claim that is not an "Excluded Claim" shall be finally resolved by binding arbitration in accordance with the Commercial Arbitration Rules and Supplementary Procedures for Large Complex Disputes of the American Arbitration Association ("AAA"), and judgment on the arbitration award may be entered in any court having jurisdiction thereof. The arbitration shall be conducted by a panel of three persons experienced in the pharmaceutical business: within 30 days after initiation of arbitration, each party shall select one person to act as arbitrator and the two party-selected arbitrators shall select a third arbitrator within 30 days of their appointment. If the arbitrators selected by the parties are unable or fail to agree upon the third arbitrator, the third arbitrator shall be appointed by the AAA. The place of arbitration shall be Denver, Colorado. Either party may apply to the arbitrators for interim injunctive relief until the arbitration award is rendered or the controversy is otherwise resolved. Either party also may, without waiving any remedy under this Agreement, seek from any court having jurisdiction any injunctive or provisional relief necessary to protect the rights or property of that party pending the arbitration award. The arbitrators shall have no authority to award punitive or any other type of damages not measured by a party's compensatory damages. Each party shall bear its own costs and expenses and attorneys' fees and an equal share of the arbitrators' and any administrative fees of arbitration. Except to the extent necessary to confirm an award or as may be required by law, neither a party nor an arbitrator may disclose the existence, content, or results of an arbitration without the prior written consent of both parties. In no event

shall an arbitration be initiated after the date when commencement of a legal or equitable proceeding based on the dispute, controversy or claim would be barred by the applicable New York statute of limitations. As used in this Section, the term "Excluded Claim" shall mean a dispute, controversy or claim that concerns (a) the validity or infringement of a patent, trademark or copyright; or (b) any antitrust, anti-monopoly or competition law or regulation, whether or not statutory.

10.7 ENTIRE AGREEMENT. This Agreement and the Clinical Supply Agreement

contain the entire understanding of the parties with respect to the license, development and commercialization of Compound and Product. All express or implied agreements and understandings, either oral or written, heretofore made by the parties on the same subject matter are expressly superseded by this Agreement. The Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by both parties hereto.

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

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

10.10 WAIVER. The waiver by either party hereto of any right hereunder, or the failure to perform, or 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.

10.11 COUNTERPARTS. The 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.

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

IN WITNESS WHEREOF, the parties have executed this Agreement as of the date(s) set forth below.

Merck & Co., Inc.	Isis Pharmaceuticals, Inc.
BY:_____	BY:_____
TITLE: _____	TITLE: _____
DATE: _____	DATE: _____

SCHEDULE 1.5

[*]

*Confidential Treatment Requested

ISIS PATENT RIGHTS

SCHEDULE 1.16 (a)(i)

[*]

and 1.16 (a)(ii)

[*]

and 1.16 (a)(iii)

[*]

*Confidential Treatment Requested 25

SCHEDULE 2.2

[*]

*Confidential Treatment Requested 26

SCHEDULE 2.2.1 (b)

[*]

*Confidential Treatment Requested 27

SCHEDULE 2.2.6

[*]

*Confidential Treatment Requested 28

SCHEDULE 2.4

[*]

*Confidential Treatment Requested 29

SCHEDULE 7.2

[*]

*Confidential Treatment Requested 30

*Text Omitted and Filed Separately
Confidential Treatment Requested
Under 17 C.F.R. Sections 200.80(b)(4)
200.83 and 240b-2

COLLABORATION AND LICENSE AGREEMENT

BY AND BETWEEN

ISIS PHARMACEUTICALS, INC.

AND

HYBRIDON, INC.

TABLE OF CONTENTS

COLLABORATION AND LICENSE AGREEMENT

This Collaboration and License Agreement (the "Agreement") is entered into as of the 24th day of May, 2001 (the "Effective Date") by and between Isis Pharmaceuticals, Inc., a corporation organized and existing under the laws of the State of Delaware ("Isis"), and Hybridon, Inc., a corporation organized and existing under the laws of the State of Delaware ("Hybridon").

INTRODUCTION

1. Hybridon is the owner or has the right to use under license certain patents and patent applications relating to the practice of Antisense Technology (as defined below).

2. Isis is the owner or has the right to use under license certain patents and patent applications relating to the practice of Antisense Technology.

3. Hybridon and Isis are interested in licensing or sublicensing to the other party these patents and patent applications and in collaborating from time to time on the further research and development of Antisense Products.

4. Hybridon and Isis have entered into a Master Agreement dated as of the date hereof (the "Master Agreement").

5. Isis and Hybridon each recognizes that the other Party has expended significant efforts and resources in the research and development of Antisense Technology and the payments to be made under the Master Agreement to each Party for the patent licenses and sublicenses granted hereunder will allow each Party to recoup such expenditures.

NOW, THEREFORE, Hybridon and Isis agree as follows:

ARTICLE I
DEFINITIONS

When used in this Agreement, each of the following terms shall have the meanings set forth in this Article I:

Section 1.1 "AFFILIATE". Affiliate shall mean, with respect to a person or entity, any corporation, company, partnership, joint venture or other entity which controls, is controlled by, or is under common control with such person or entity. For purposes of this Section 1.1 and Section 1.21, "control" shall mean (a) in the case of corporate entities, direct or indirect ownership of fifty percent (50%) or more of the stock or shares having the right to vote for the election of directors, and (b) in the case of non-corporate entities, direct or indirect ownership of fifty percent (50%) or more of the equity interest with the

power to direct the management and policies of such non-corporate entities, provided that in either such case such person or entity has the power to direct the management and policies of such entities, whether by contract or through representation on the board of directors or other governing body of such entities.

Section 1.2 "AMINO PATENT RIGHTS". Amino Patent Rights shall mean the claims of all patents and patent applications set forth on EXHIBIT A hereto and any continuations or divisions thereof, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

Section 1.3 "ANTISENSE PRODUCTS". Antisense Products shall mean oligonucleotides or oligonucleotide analogs or mimics thereof targeted to a specific sequence of RNA that hybridize to such sequence and through such hybridization modulate the production of the targeted gene product. The term Antisense Products shall not include Ribozymes.

Section 1.4 "ANTISENSE TECHNOLOGY". Antisense Technology shall mean the use of any oligonucleotide or oligonucleotide analog or mimic thereof targeted to a specific sequence of RNA that hybridizes to such sequence and through such hybridization modulates the production of the targeted gene product. The term Antisense Technology shall not include Ribozyme Technology.

Section 1.5 "CONFIDENTIAL INFORMATION". Confidential Information shall mean all information, including, without limitation, proprietary information and materials (whether or not patentable) regarding a Party's technology, products, business information or objectives, which is designated as confidential in writing by the disclosing Party, whether by letter or by the use of an appropriate stamp or legend, prior to or at the time any such information is disclosed by the disclosing Party to the other Party. Notwithstanding the foregoing, all information which is orally, electronically or visually disclosed by a Party, or is disclosed in writing without an appropriate letter, stamp or legend, shall constitute Confidential Information of a Party if the disclosing Party, within thirty (30) days after such disclosure, delivers to the other Party a written document or documents describing the information and referencing the place and date of such oral, visual, electronic or written disclosure and the names of the persons to whom such disclosure was made.

Section 1.6 "DOCKET 104". Docket 104 shall mean all patents and patent applications set forth on EXHIBIT B-1 hereto and any continuations or divisions thereof, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any

supplemental patent certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

Section 1.7 "DOCKET 105". Docket 105 shall mean all patents and patent applications set forth on EXHIBIT B-2 hereto and any continuations or divisions thereof, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

Section 1.8 "DRUG POTENTIATION PATENT RIGHTS". Drug Potentiation Patent Rights shall mean the claims of all patents and patent applications set forth on EXHIBIT M hereto and any continuations or divisions thereof, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such

patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

Section 1.9 "EXHIBIT K PATENTS". Exhibit K Patents shall mean the claims of all patents and patent applications set forth on EXHIBIT K hereto and any continuations or divisions thereof, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

Section 1.10 "FACILITATOR PATENT RIGHTS". Facilitator Patent Rights shall mean the claims of all patents and patent applications set forth on EXHIBIT C hereto and any continuations or divisions thereof, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

Section 1.11 "FINDERON PATENT RIGHTS". Finderon Patent Rights shall mean the claims of all patents and patent applications set forth on EXHIBIT D hereto and any continuations or divisions thereof, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

Section 1.12 "HYBRIDON ANTISENSE DRUG". Hybridon Antisense Drug shall mean an Antisense Product which is a therapeutic or prophylactic product for the treatment or prevention of disease in a human or an animal that is discovered,

developed and/or Optimized either by Hybridon or a Subsidiary alone or as part of a "bona fide drug discovery collaboration".

For purposes of this Section 1.12 only, a "bona fide drug discovery collaboration" is an arrangement between Hybridon or a Subsidiary and a third party (i) in which the intent of the collaborators in engaging in discovery, development and/or Optimization activities is to discover, develop, Optimize and commercialize an Antisense Product. [*] Initiation of IND supporting toxicology is the initiation of animal toxicity studies in support of the filing of an Investigational New Drug application with the U.S. Food and Drug Administration or a similar regulatory filing with a similar regulatory authority in another jurisdiction. If a contractor (which is not the third party collaborator) in the business of performing preclinical studies provides such services through the performance of IN VIVO animal studies under the supervision of Hybridon or a Subsidiary, the services so provided shall be treated as work performed directly by Hybridon or a Subsidiary for purposes of this definition. Work performed by a contractor of, and paid for by, Hybridon or a Subsidiary under the supervision of Hybridon or a Subsidiary shall be treated as work performed directly by Hybridon or a Subsidiary for purposes of this definition. The Parties acknowledge that a part of the discovery, development and Optimization of an Hybridon Antisense Drug may involve the validation and prioritization of gene targets to form the basis for antisense drug discovery activities.

In the event of a sale or other transfer of the assets of Hybridon, no Antisense Product developed by the acquiring company prior to the acquisition will be deemed to be a Hybridon Antisense Drug unless (i) such acquiring company acquires all or substantially all of the assets of the antisense business of Hybridon, and (ii) such Antisense Product [*]by the acquiring company prior to the acquisition; provided, however, that an Antisense Product that would qualify as a Hybridon Antisense Drug irrespective of the acquisition will not lose its status as such as a result of such acquisition.

Section 1.13 "HYBRIDON ANTISENSE PATENT RIGHTS". Hybridon Antisense Patent Rights shall mean the claims of all patents and patent applications and any continuations or divisions thereof, whether now existing, now filed or later filed on inventions invented, licensed or sublicensed by Hybridon prior to April 26, 2001, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing, which Hybridon owned or had the right to sublicense as of April 26, 2001 and which are necessary or useful to practice Antisense Technology, including without limitation the patents and patent applications set

forth on EXHIBIT E, but not including the Hybridon Excluded Patent Rights and the patents and patent

applications licensed to Hybridon (the "Hybridon IDT Patent Rights") pursuant to the Non-Exclusive License Agreement dated as of March 12, 1999 between Integrated DNA Technologies, Inc. ("IDT") and Hybridon.

Section 1.14 "HYBRIDON EXCLUDED PATENT RIGHTS". Hybridon Excluded Patent Rights shall mean the Amino Patent Rights, Docket 104, Docket 105, Facilitator Patent Rights, Finderon Patent Rights, Immune Stimulation Patent Rights, Drug Potentiation Patent Rights and the Exhibit K Patents.

Section 1.15 "HYBRIDON INTELLECTUAL PROPERTY". Hybridon Intellectual Property shall mean collectively the Hybridon Antisense Patent Rights and the Hybridon Excluded Patent Rights (all solely to the extent licensed to Isis under Section 2.1), but shall exclude the Hybridon IDT Patent Rights.

Section 1.16 "IMMUNE STIMULATION PATENT RIGHTS". Immune Stimulation Patent Rights shall mean the claims of all patents and patent applications set forth on EXHIBIT F hereto and any continuations or divisions thereof, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

Section 1.17 "ISIS INTELLECTUAL PROPERTY RIGHTS". Isis Intellectual Property Rights shall mean the claims that cover Motifs or RNaseH Dependent Mechanisms of Action of all patents and patent applications and any continuations or divisions thereof, whether now existing, now filed or later filed on inventions invented, licensed or sublicensed by Isis prior to April 26, 2001, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplemental patent certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing, which Isis owned or had the right to sublicense as of April 26, 2001, including without limitation the patents and patent applications set forth on EXHIBIT G hereto; provided, however, that Isis Intellectual Property Rights shall not include manufacturing methods, including without limitation reagents, synthons and processes used in manufacturing and analyzing oligonucleotides; chemistries, including without limitation modifications made to the backbone, sugar or base of an oligonucleotide and oligonucleotide conjugates (including the chemistries of the conjugate and the conjugation methods); formulations, including without limitation methods and reagents for delivery and uptake of oligonucleotides; gene-related patents, including without limitation patents to specific gene structures, gene targets and treatments based upon a genetic target; and patents and patent applications licensed to

Isis pursuant to the Non-Exclusive License Agreement dated March 19, 1999 between IDT and Isis.

Section 1.18 [*]

Section 1.19 "MOTIFS". Motifs shall mean hybrid oligonucleotide structures that have at least two regions within the oligonucleotide that have different chemistries, one of which will support cleavage via RNaseH Dependent Mechanisms of Action. Motifs do not include specific chemistries necessary or useful to create or Optimize such structures, whether or not such chemistries are also disclosed by or claimed in the same patent or patent application.

Section 1.20 "NAKED SUBLICENSE". Naked Sublicense shall mean any license or sublicense of intellectual property granted by a Party or a Subsidiary to a third party other than a license or sublicense which is granted as part of a bona fide research, development, manufacturing or commercialization collaboration between the Party or a Subsidiary and the third party (it being agreed by the Parties that the definition of the term "collaboration" in this Section 1.20 shall not be interpreted by reference to the definition of collaboration used in Section 1.12). For purposes of this definition, a bona fide research, development, manufacturing or commercialization collaboration may include collaborative research and discovery, including without limitation gene functionalization and target validation.

Section 1.21 "NON-PARENT AFFILIATE". Non-Parent Affiliate shall mean, with

respect to a person or entity, any Affiliate of such person or entity other than any corporation, company, partnership, joint venture or other entity which controls (as defined in Section 1.1) such person or entity.

Section 1.22 "OPTIMIZATION". Optimization shall mean the process by which the properties of an Antisense Product are improved by making chemical modifications to such Antisense Product or by selecting a different sequence of RNA for such Antisense Product.

Section 1.23 "PARTY". Party shall mean Isis or Hybridon; "Parties" shall mean Isis and Hybridon. As used in this Agreement, references to "third parties" do not include a Party or its Subsidiaries.

Section 1.24 "RIBOZYMES". Ribozymes shall mean oligonucleotides or oligonucleotide analogs or mimics containing a catalytic core having a bulge or stem loop and regions flanking the catalytic core that hybridize to a targeted RNA and modulate the targeted RNA by cleavage at a site next to a specific ribonucleotide triplet by an oligonucleotide catalyzed transesterification reaction.

Section 1.25 "RIBOZYME TECHNOLOGY". Ribozyme Technology shall mean the use of any oligonucleotides or oligonucleotide analogs or mimics thereof containing a catalytic core having a bulge or stem loop and regions flanking the catalytic core that hybridize to a targeted RNA and modulate the

targeted RNA by cleavage at a site next to a specific ribonucleotide triplet by an oligonucleotide catalyzed transesterification reaction.

Section 1.26 "RNASEH DEPENDENT MECHANISMS OF ACTION". RNaseH Dependent Mechanisms of Action shall mean methods of using RNaseH enzymes to cleave a targeted RNA in vitro or in vivo. RNaseH Dependent Mechanisms of Action do not include chemistries necessary or useful to facilitate or Optimize such cleavage, whether or not such chemistries are also disclosed by or claimed in the same patent or patent application.

Section 1.27 "SUBLICENSE INCOME". Sublicense Income shall mean all consideration received from Sublicensees by Isis or a Subsidiary pursuant to a Naked Sublicense by Isis or a Subsidiary which covers, in whole or in part, Hybridon Intellectual Property and all consideration received from Sublicensees by Isis or an Affiliate pursuant to a Naked Sublicense not involving Hybridon Intellectual Property if such Naked Sublicense arose out of the same transaction as, or was otherwise related to, a Naked Sublicense which covers, in whole or in part, Hybridon Intellectual Property. Sublicense Income does not include (i) payments made by a Sublicensee in consideration for the issuance of equity or debt securities of Isis to the extent such payments do not exceed the fair market value of the securities being issued. [*] If non-monetary consideration is received from Sublicensees by Isis or its Subsidiaries, then a commercially reasonable monetary value will be assigned for purposes of calculating Sublicense Income.

Section 1.28 "SUBLICENSEE". Sublicensee shall mean any third party granted the right hereunder by a Party, its Subsidiaries or a Sublicensee having the right to grant further sublicenses, to discover, develop, make, have made, use, sell, have sold, offer to sell, import or have imported products covered by the Hybridon Intellectual Property (in the case of a Sublicensee of Isis, its Subsidiaries or a Sublicensee having the right to grant further sublicenses) or Isis Intellectual Property or Tullis Patents (in the case of a Sublicensee of Hybridon, its Subsidiaries or a Sublicensee having the right to grant further sublicenses).

Section 1.29 "SUBSIDIARY". Subsidiary shall mean with respect to a Party, any corporation, company, partnership, joint venture or other entity, 100% of the equity securities of which are directly or indirectly owned by such Party; provided, however, that if such Party does not directly or indirectly own 100% of the equity securities of the entity, such entity shall nevertheless be deemed a Subsidiary for purposes of this definition if the equity securities not owned directly or indirectly by such Party consist solely of: (a) director qualifying shares, (b) equity securities of the entity owned by employees, directors or officers of the Party or the entity so long as such ownership by employees, directors and officers does not exceed 10% of the equity securities of the entity and/or (c) in the case of entities, the operations of which are substantially conducted outside the United States, equity securities of the entity owned by financial investors so long as such ownership by financial investors does not exceed 20% of the equity securities of the entity. For

purposes of this Section 1.29, indirect ownership shall mean ownership through an entity or a chain

Section 1.30 of entities as to each member of which the Party or another entity in the chain owns 100% of the equity securities (other than director qualifying shares).

Section 1.31 "THIRD PARTY LICENSE AGREEMENTS". Third Party License Agreements shall mean those agreements set forth on EXHIBIT H-1 attached hereto pursuant to which Hybridon has licensed Hybridon Intellectual Property to third parties.

Section 1.32 "TULLIS NET SALES". Tullis Net Sales shall mean the gross sales revenues received by Hybridon, its Subsidiaries or Sublicensees from the sale of Tullis Products, minus (a) all sales, use, and excise taxes, and customs duties or other charges; (b) transportation and handling charges (including transport insurance) actually incurred and paid by the buyer as part of the purchase price; and (c) amounts repaid or credited by reason of rejections or returns. Sales of a Tullis Product by Hybridon to a Subsidiary of Hybridon for sale by the Subsidiary shall not be considered a sale of Tullis Products hereunder.

Section 1.33 "TULLIS PATENTS". Tullis Patents shall mean the Technology Rights (as defined in the Non-Exclusive Patent License Agreement dated September 14, 1992 (the "Tullis Agreement") between Isis and Molecular Biosystems, Inc. ("MBI")) licensed by Isis from MBI under the Tullis Agreement, including without limitation the patents and patent applications set forth on EXHIBIT I hereto.

Section 1.34 "TULLIS PRODUCT". Tullis Product shall mean any product whose use, manufacture or sale by Hybridon, its Subsidiaries or Sublicensees, in any jurisdiction in which a patent which is a Tullis Patent has been allowed, would but for the provisions of Section 3.3 constitute an infringement of such patent.

Section 1.35 "UMASS PATENT RIGHTS". UMass Patent Rights shall mean the Patent Rights (as defined in the UMass Agreement (as defined below)) licensed by Hybridon from UMass under the UMass Agreement, including without limitation the patents and patent applications set forth on EXHIBIT L hereto.

Section 1.36 "VALID CLAIM". Valid Claim shall mean a claim which (i) in the case of any unexpired United States or foreign patent, shall not have been donated to the public, disclaimed or held invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision, or (ii) in the case of any United States or foreign patent application, shall not have been permanently cancelled, withdrawn, abandoned or been pending for more than seven (7) years.

ARTICLE II
GRANT OF RIGHTS BY HYBRIDON

Section 2.1 LICENSE GRANT.

(a) License Grant to Hybridon Antisense Patent Rights. Subject to the terms and conditions of this Agreement, including without limitation Hybridon's retained rights under Section 2.3 and Section 2.5(a) of this Agreement, Hybridon hereby grants to Isis and its Subsidiaries an exclusive worldwide license or sublicense, as applicable, under the Hybridon Antisense Patent Rights, to practice Antisense Technology and to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products. These rights shall only be sublicensable as explicitly provided in Section 2.2.

(b) Limited License Grant to Hybridon Excluded Patent Rights. Subject to the terms and conditions of this Agreement, including without limitation Hybridon's retained rights under Section 2.3 and Section 2.5(a) of this Agreement, Hybridon hereby grants to Isis and its Subsidiaries the limited worldwide licenses or sublicenses, as applicable, under the Hybridon Excluded Patent Rights to practice Antisense Technology and to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products, in each case solely to the extent specifically described below. These rights shall only be sublicensable as explicitly provided in Section 2.2.

(i) [*]

(ii) [*]

(iii) under the Immune Stimulation Patent Rights (A) to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products which contain modifications which have neutralized the immune stimulation caused by an immunostimulatory CpG dinucleotide in such Antisense Products, (B) to practice Antisense Technology using oligonucleotides which contain modifications which have neutralized the immune stimulation caused by an immunostimulatory CpG dinucleotide in such oligonucleotides, and (C) to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products which target genes involved in immunity modulation;

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(iv) under the Facilitator Patent Rights to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology, provided that neither such Antisense Products nor such Antisense Technology use, or are used with, a Ribozyme or Ribozyme Technology;

(v) under the Finderon Patent Rights to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology, provided that neither such Antisense Products nor such Antisense Technology use, or are used with, a Ribozyme or Ribozyme Technology;

(vi) under the Amino Patent Rights to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology, provided that such Antisense Products and Antisense Technology use, or are used with, the technology covered by the claims of the Amino Patent Rights solely for the conjugation of functional groups for therapeutic or prophylactic purposes only;

(vii) under the Drug Potentiation Patent Rights to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology, which Antisense Products and Antisense Technology primarily act against a gene target implicated in cancer through an antisense mechanism, but which may incidentally potentiate an anti-cancer prodrug; and

(viii) under the Exhibit K Patents to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology; provided, however, that the license contemplated by this clause (viii) shall not extend to Antisense Products or Antisense Technology related to specific claimed gene targets or pseudo-cyclic oligonucleotide structures and applications.

The Parties agree that if, during the term of the license and sublicense granted by Hybridon to Isis and its Subsidiaries in this Section 2.1(b), a claim

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issues from any patent application included in Hybridon Excluded Patent Rights that is necessary or useful for the practice of Antisense Technology, Hybridon shall not use such claim to preclude or otherwise interfere with the ability of Isis or its Subsidiaries to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products and practice Antisense Technology; provided, however, that to the extent that the license or sublicense grant set forth above in this Section 2.1(b) is limited in scope as to its application to Antisense Products or Antisense Technology, such limitation shall also be applicable to the restrictions on Hybridon's rights to preclude or otherwise interfere with Isis and its Subsidiaries set forth in this paragraph (i.e., if the license or sublicense grant is not applicable, Hybridon shall not be restricted from precluding or interfering).

(c) The licenses and sublicenses granted by Hybridon to Isis and its Subsidiaries in Sections 2.1(a) and (b) to the extent such licenses or sublicenses cover UMass Patent Rights are subject to, without limitation Sections 2.2(a), 2.2(b), 2.2(d), 2.6, 2.7, 4.3(a), 4.3(d), 7.1, 10.4 and 12.4(a) of the License Agreement dated as of February 21, 1990 and restated as of September 8, 1993 by and between Hybridon and University of Massachusetts Medical Center (formerly the Worcester Foundation for Biomedical Research, Inc. and referred to herein as "UMass") (the "UMass Agreement"). A copy of the UMass Agreement is attached to this Agreement as EXHIBIT J. Hybridon hereby represents and warrants as of the date hereof: (i) that Exhibit J is a true, correct and complete copy of the UMass Agreement and all amendments and/or other changes thereto, (ii) that the UMass Agreement is in full force and effect, (iii) that Hybridon is not in default thereunder and (iv) that there has been no waiver of rights by Hybridon thereunder. Hybridon further represents and warrants as of the date hereof that Isis shall have no payment obligation to UMass arising out of the execution and delivery of this Agreement or the sublicensing by Hybridon of the UMass Patent Rights hereby and that any payment obligations that do arise under the UMass Agreement shall be the sole responsibility of Hybridon; provided that Isis may have payment obligations to UMass directly in the case of a termination of the UMass Agreement pursuant to the last paragraph of Section 2.2(c) of the UMass Agreement.

Section 2.2 SUBLICENSING RIGHT.

(a) Isis and its Subsidiaries shall have the right to grant sublicenses under the licenses and sublicenses from Hybridon set forth in Section 2.1 above to third parties. Each such sublicense shall be subject and subordinate to, and consistent with, the terms and conditions of this Agreement, and shall provide that any Sublicensee shall have no right to grant further sublicenses except on terms consistent with this Section 2.2. In the event of a material default by any

Sublicensee under a sublicense agreement, Isis will inform Hybridon and take commercially reasonable efforts to cause the Sublicensee to cure the default or will terminate the sublicense or, if Isis is not the sublicensor under such sublicense, Isis will cause the sublicensor under such sublicense to take commercially reasonable efforts to cause the Sublicensee to cure the default or to terminate such sublicense; provided, however that none of Isis, its Subsidiaries or the sublicensor under such sublicense shall be responsible to Hybridon for the default by the Sublicensee under the sublicense agreement.

(b) (i) Isis shall provide UMass with a copy of any sublicense granted pursuant to this Section 2.2 by Isis or its Subsidiaries or Sublicensees which includes a sublicense of UMass Patent Rights, within thirty (30) days after the grant of such sublicense. Hybridon shall use its reasonable best efforts to cause UMass to enter into a confidentiality agreement with Isis with respect to sublicenses provided to UMass under this clause (i) (it being understood that Hybridon shall not be obligated to make any payment or to provide any other consideration to UMass for such confidentiality agreement by UMass).

(ii) Isis shall provide Hybridon with written notice of any sublicense (an "Isis Sublicense") granted pursuant to this Section 2.2 by Isis or its Subsidiaries or Sublicensees within thirty (30) days after the grant of such sublicense, such written notice specifying the name of the Sublicensee, the date of the sublicense and whether such Isis Sublicense includes UMass Patent Rights or is a Naked Sublicense. Hybridon shall have the right, not more than twice during any calendar year, to have any Isis Sublicense reviewed by an independent third party chosen by Hybridon to ascertain whether such Isis Sublicense includes UMass Patent Rights or is a Naked Sublicense. Isis shall cooperate in all reasonable respects with the review of such Isis Sublicense by the independent third party under this Section 2.2(b)(ii), including without limitation responding to questions directed at determining whether such Isis Sublicense includes UMass Patent Rights or is a Naked Sublicense. Hybridon shall pay all costs of such review; provided, however, that if, contrary to the information provided by Isis in the written notice provided to Hybridon in connection with the grant of such Isis Sublicense, such Isis Sublicense does in fact include UMass Patent Rights or is a Naked Sublicense, Isis shall reimburse Hybridon for the costs of such review. If the independent third party determines that such Isis Sublicense includes UMass Patent Rights or is a Naked Sublicense, such independent third party shall notify Isis and Hybridon. If Isis disagrees with the determination of the independent third party, the third party shall be permitted hereunder to provide Hybridon with a copy of the Isis Sublicense.

(c) Any Naked Sublicense of Hybridon Intellectual Property by Isis or its Subsidiaries to (i) third parties which are parties to license or sublicense agreements with Isis or its Affiliates or Subsidiaries not involving Hybridon Intellectual Property and (ii) Affiliates of Isis or its Subsidiaries shall be made by Isis or its Subsidiaries on commercially reasonable terms. Isis and its Subsidiaries shall not sublicense Hybridon Intellectual Property separately from any intellectual property of Isis or its Affiliates or Subsidiaries, including without limitation the Isis Intellectual Property, for the purpose of reducing the amount of Sublicense Income payable by Isis or its Subsidiaries to Hybridon under Section 4.3.

Section 2.3 NO IMPLIED LICENSES; RETAINED RIGHTS. Other than those rights and licenses explicitly granted herein, no right or license under the Hybridon Intellectual Property is granted to Isis or its Subsidiaries or Sublicensees. Notwithstanding the rights and licenses granted herein, Hybridon shall retain its rights under the Hybridon Intellectual Property for all purposes, including without limitation its rights to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Antisense Products, to practice Antisense Technology and to license or sublicense Hybridon Intellectual Property; provided, that, except for licenses and sublicenses provided under the Third Party License Agreements, Hybridon and its Subsidiaries shall not grant any Naked Sublicenses of the Hybridon Antisense Patent Rights to any third parties (other than Subsidiaries).

Section 2.4 COMMERCIALIZATION EFFORTS. Isis hereby agrees to undertake reasonable efforts to bring one or more products covered by a claim of the UMass Patent Rights into commercial use as quickly as is reasonably possible.

Section 2.5 LICENSE AGREEMENTS TO WHICH HYBRIDON IS A PARTY.

(a) Notwithstanding Section 2.1 of this Agreement, Hybridon shall not and is not licensing or sublicensing to Isis or its Subsidiaries any rights under the Hybridon Intellectual Property to the extent that such Hybridon Intellectual Property has been licensed or sublicensed by Hybridon under the Third Party License Agreements.

(b) Hybridon hereby represents and warrants as of the date hereof that, except for the agreements set forth on EXHIBIT H-2 attached hereto: (i) Hybridon has not entered into any agreement under which it has licensed from another party any of the Hybridon Intellectual Property and (ii) Hybridon has not entered into any agreement under which it has licensed to another party any of the Hybridon Intellectual Property other than the Third Party License Agreements.

(c) Hybridon agrees that it shall not amend or expand any Third Party License Agreement in a manner that is inconsistent with this Agreement, including without limitation amending any Third Party License Agreement to grant any new exclusive license under the Hybridon Antisense Patent Rights, without the prior written consent of Isis, which consent shall not be unreasonably withheld or delayed.

(d) Hybridon hereby represents and warrants as of the date hereof as to the Third Party License Agreements: (i) that it has provided true

and correct copies of all such agreements to Isis, (ii) that all such agreements are in full force and effect, (iii) that Hybridon is not in default under any such agreement and (iv) that there has been no waiver of rights by Hybridon thereunder.

Section 2.6 METHYLGENE LICENSE AGREEMENT. If Methylgene Inc. ("Methylgene") designates a target which Methylgene desires to select as a Second Molecular Target or a Third Molecular Target (as such terms are defined in the Amended and Restated License Agreement made effective as of January 4, 1996, as amended and restated on September 21, 2000 (the "Methylgene License Agreement")) pursuant to the terms of the Methylgene License Agreement [*].

Section 2.7 ORIGENIX LICENSE AGREEMENT. Hybridon shall [*] License Agreement dated as of January 22, 1999 (the "OriGenix License Agreement") between Hybridon and OriGenix Technologies Inc. ("OriGenix")) and shall [*]

Section 2.8 AFFILIATES. Hybridon hereby represents and warrants as of the

date hereof that no Affiliate of Hybridon owns or controls any patents, patent applications or inventions invented, licensed or sublicensed by such Affiliate prior to April 26, 2001 which are necessary or useful to practice Antisense Technology.

ARTICLE III
GRANT OF RIGHTS BY ISIS

Section 3.1 LICENSE GRANT. Subject to the terms and conditions of this Agreement, Isis hereby grants to Hybridon and its Subsidiaries a worldwide non-exclusive license or sublicense, as applicable under the Isis Intellectual Property Rights to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Hybridon Antisense Drugs. These rights shall only be sublicensable as explicitly provided in Section 3.2.

Section 3.2 SUBLICENSING RIGHT. Hybridon and its Subsidiaries shall have the right to grant sublicenses under the license from Isis set forth in Section 3.1 above to third parties only to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Hybridon Antisense Drugs. Each such sublicense shall be subject and subordinate to, and consistent with, the terms and conditions of this Agreement, and shall provide that any Sublicensee shall have no right to grant further sublicenses except on

terms consistent with this Section 3.2. In the event of a material default by any Sublicensee under a sublicense agreement, Hybridon will inform Isis and take commercially reasonable efforts to cause the Sublicensee to cure the default or will terminate the sublicense or, if Hybridon is not the sublicensor under such sublicense, Hybridon will cause the sublicensor under such sublicense to take commercially reasonable efforts to cause the Sublicensee to cure the default or to terminate such sublicense; provided however that none of Hybridon, its Subsidiaries or the sublicensor under such sublicense shall be responsible to Isis for the default by the Sublicensee under the sublicense agreement. Notwithstanding the rights granted under this Section 3.2, Hybridon and its Subsidiaries shall [*]

Section 3.3 TULLIS PATENTS.

(a) Subject to the terms and conditions of this Agreement, Isis hereby grants to Hybridon and its Subsidiaries a worldwide non-exclusive sublicense, with the right to grant sublicenses as provided in Section 3.3(b), under the Tullis Patents to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Hybridon Antisense Drugs, provided that such Hybridon Antisense Drugs employ technology covered by the Isis Intellectual Property as a material element thereof.

(b) (i) Hybridon and its Subsidiaries shall have the right to grant sublicenses under the license from Isis set forth in Section 3.3(a) to third parties (x) provided that such sublicense may only be granted to third parties in connection with the grant of a sublicense to such third parties of Isis Intellectual Property under Section 3.2, and (y) solely to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Hybridon Antisense Drugs that employ technology covered by the Isis Intellectual Property as a material element thereof. Each such sublicense shall be subject and subordinate to, and consistent with, the terms and conditions of this Agreement, and shall provide that any such Sublicensee shall have no right to grant further sublicenses except on terms consistent with this Section 3.3(b).

(ii) Hybridon shall provide MBI with a copy of any sublicense granted by Hybridon or its Subsidiaries or Sublicensees pursuant to this Section 3.3(b) within thirty (30) days after the grant of such sublicense. Isis shall use its reasonable best efforts to cause MBI to enter into a confidentiality agreement with Hybridon with respect to sublicenses provided to MBI under this Section 3.3(b) (it being understood that Isis shall not be obligated to make any payment or to provide any other consideration to MBI for such confidentiality agreement by MBI). In the event that MBI does not sign such a confidentiality agreement with Hybridon, Isis shall enforce against MBI, for and on behalf of Hybridon, the confidentiality provisions of the Tullis

Agreement with respect to the sublicenses provided by Hybridon, its Subsidiaries or Sublicensees to MBI and with respect to any other confidential information of Hybridon or a Subsidiary or Sublicensee of Hybridon that MBI receives.

(iii) In the event of a material default by any

Sublicensee under a sublicense agreement pursuant to this Section 3.3(b), Hybridon will inform Isis and take commercially reasonable efforts to cause the Sublicensee to cure the default or will terminate the sublicense, or if Hybridon is not the sublicensor under such sublicense, Hybridon will cause the sublicensor under such sublicense to take commercially reasonable efforts to cause the Sublicensee to cure the default or to terminate such sublicense; provided however that none of Hybridon, its Subsidiaries or the sublicensor under such sublicense shall be responsible to Isis for the default by the Sublicensee under the sublicense agreement. Notwithstanding the rights granted under this Section 3.3(b), Hybridon shall [*]

(c) A copy of the Tullis Agreement is attached to this Agreement as EXHIBIT N. Isis hereby represents and warrants as of the date hereof: (i) that Exhibit N is a true, correct and complete copy of the Tullis Agreement and all amendments and/or other changes thereto that affect the rights of Hybridon as a sublicensee thereunder, (ii) that the Tullis Agreement is in full force and effect, (iii) that Isis is not in default thereunder and (iv) that there has been no waiver of rights by Isis thereunder. Isis further represents and warrants as of the date hereof that Hybridon shall have no payment obligation to MBI arising out of the execution and delivery of this Agreement or the sublicensing by Isis of the Tullis Patents hereby and that any payment obligations that do arise shall be the sole responsibility of Isis.

Section 3.4 SCOPE OF LICENSE. Hybridon acknowledges that Isis claims intellectual property covering numerous chemical modifications to oligonucleotides including without limitation modifications to backbone linkages, sugars, heterocyclic bases and conjugates and to methods of making the same, including methods of making various oligonucleotide intermediates (the "Isis Chemistry Intellectual Property"). Hybridon acknowledges and agrees that no Isis Chemistry Intellectual Property is included in the Isis Intellectual Property being licensed or sublicensed to Hybridon and its Subsidiaries pursuant to Section 3.1 of this Agreement, except as expressly set forth below in this Section 3.4. [*] Isis hereby agrees that any patents owned or controlled by Isis or an Affiliate as of the date hereof or any patents that may issue in the future to Isis or an Affiliate from or in respect of any patent applications which Isis or an Affiliate owned or had the right to sublicense as of April 26, 2001, which would otherwise be infringed by the practice of the Hybridon 2'-O Methyl Chemistry, shall constitute Isis Intellectual Property for all purposes of this Agreement, including without limitation the license grant provided in Section

3.1; provided, however, that the license grant with respect to such patents shall only provide Hybridon and its Subsidiaries with the right to discover, develop, make, have made, use, sell, have sold, offer to sell, import and have imported Hybridon Antisense Drugs which incorporate the Hybridon 2'-O

Methyl Chemistry. If any patent of Isis or an Affiliate includes claims to a combination of modifications to both substitution with 2'-O-methyl and Isis Chemistry Intellectual Property in addition to 2'-O-methyl substituents, nothing in this Section 3.4 shall be deemed to be a grant of rights to Hybridon or its Subsidiaries to practice the Isis Chemistry Intellectual Property other than 2'-O-methyl substituents.

Section 3.5 NO IMPLIED LICENSES. Other than those rights and licenses explicitly granted herein, no right or license under the Isis Intellectual Property or the Tullis Patents is granted to Hybridon or its Subsidiaries or Sublicensees.

Section 3.6 LIMITATION ON LICENSE GRANT WITH RESPECT TO TARGET VALIDATION AND GENE FUNCTIONALIZATION ACTIVITIES. Notwithstanding anything to the contrary in Sections 3.1 and 3.3(a), the licenses set forth in Sections 3.1 and 3.3(a) above do not grant Hybridon and its Subsidiaries the right:

(a) to use the Isis Intellectual Property and the Tullis Patents for target validation and gene functionalization activities, except when, and only to the extent that, (i) such activities are directed to the discovery, development, Optimization and commercialization of a Hybridon Antisense Drug and (ii) such activities are performed only by Hybridon or a Subsidiary and not by a contractor or a collaborator, or

(b) to use, or enable any third party to use, any information that is developed during such target validation and gene functionalization activities in the development of a drug other than a Hybridon Antisense Drug, including without limitation, small molecules, ribozymes, proteins

and pseudocyclic oligonucleotide structures.

Section 3.7 NOTICE OF HYBRIDON ANTISENSE DRUGS. Hybridon shall provide Isis with written notice of any Hybridon Antisense Drugs developed under a sublicense granted by Hybridon or its Subsidiaries under Section 3.2 (a "Hybridon Antisense Drug Sublicense") promptly after such Hybridon Antisense Drug is developed. Isis shall have the right, not more than twice during any calendar year, to have any Hybridon Antisense Drug Sublicense reviewed by an independent third party chosen by Isis to confirm whether such Hybridon Antisense Drug qualifies as a Hybridon Antisense Drug as defined under this Agreement. Hybridon shall cooperate in all reasonable respects with the review of such Hybridon Antisense Drug Sublicense by the independent third party under this Section 3.6, including without limitation responding to questions directed at determining whether such Hybridon Antisense Drug qualifies as a Hybridon Antisense Drug. Isis shall pay all costs of such review; provided, however, that if such Hybridon Antisense Drug does not qualify as a Hybridon Antisense Drug as defined under this Agreement, Hybridon shall reimburse Isis for the costs of such review. If the independent third party determines that such Hybridon Antisense Drug does not qualify as

a Hybridon Antisense Drug as defined under this Agreement, such independent third

party shall notify Hybridon and Isis. If Hybridon disagrees with the determination of the independent third party, the third party shall be permitted to provide Isis with a copy of the Hybridon Antisense Drug Sublicense.

Section 3.8 AFFILIATES. Isis hereby represents and warrants as of the date hereof that no Affiliate of Isis owns or controls any patents, patent applications or inventions invented, licensed or sublicensed by such Affiliate prior to April 26, 2001 which cover or claim Motifs or RNaseH Dependent Mechanisms of Action.

ARTICLE IV
PAYMENT OBLIGATIONS

Section 4.1 CONSIDERATION FOR LICENSES OF HYBRIDON INTELLECTUAL PROPERTY AND ISIS INTELLECTUAL PROPERTY. In consideration of the licenses and sublicenses granted under Sections 2.1 and 3.1 of this Agreement and the restrictions on use agreed to by Hybridon under this Agreement, Hybridon and Isis each shall pay to the other the consideration set forth in the Master Agreement and Section 4.2 and Section 4.3 of this Agreement. Isis and Hybridon each recognizes that the other Party has expended significant efforts and resources in the research and development of Antisense Technology and the payments to be made under the Master Agreement to each Party for the patent licenses and sublicenses granted hereunder will allow each Party to recoup such expenditures.

Section 4.2 CONSIDERATION FOR SUBLICENSE OF TULLIS PATENTS. In consideration of the sublicense granted by Isis to Hybridon under Section 3.3 of this Agreement, Hybridon shall pay to Isis the annual maintenance fee and royalties provided below:

(a) On the date hereof and each anniversary of such date thereafter (until the earlier of the termination of the sublicense grant under Section 3.3 or the date on which there ceases to be any Valid Claims included in the Tullis Patents), an annual maintenance fee of [*]

(b) Hybridon shall pay to Isis earned royalties at the rate of [*] of Tullis Net Sales of Tullis Products. Hybridon shall be obligated to pay such royalties on a country-by-country basis, so long as there continues to be a Valid Claim included in the Tullis Patents which covers the manufacture, use or sale of the applicable Tullis Product in such country. During the term of the sublicense under Section 3.3 and for so long thereafter as Hybridon is required to report royalties payable under this Section 4.2, Hybridon shall deliver to Isis within thirty (30) days after March 31, June 30, September 30 and December 31 of each year a report indicating (i) Tullis Net Sales for each Tullis Product, on a Tullis

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Product-by-Tullis Product and country-by-country basis, including an accounting of the deductions from Tullis Net Sales permitted by the

definition thereof and (ii) total royalties owed. Simultaneously with the delivery of each such report, Hybridon shall pay to Isis the royalty payments due under this Agreement for the period covered by such report. If no royalties are due, it shall be so reported.

Section 4.3 ISIS SUBLICENSE INCOME. Isis shall pay to Hybridon [*] of all Sublicense Income, [*] in respect of Sublicense Income received in connection with a Naked Sublicense [*]. Such payment by Isis shall be paid to Hybridon within 30 days after the calendar quarter in which the Sublicense Income was received by Isis or a Subsidiary. Isis shall deliver to Hybridon with such payment a report describing such Sublicense Income and how such Sublicense Income was calculated, all on a country-by-country and product-by-product basis.

Section 4.4 RECORDS; AUDITS. For a period not less than three (3) years after the relevant period, each Party shall keep full, true and accurate books of account sufficient to determine the amounts payable pursuant to Section 4.2(b) or 4.3, as the case may be. Each Party shall have the right, not more than once during any calendar year, to have the books and records of the other Party audited by a qualified independent accounting firm of its choosing, under appropriate confidentiality provisions, to ascertain the accuracy of the reports and payments hereunder and compliance by the other Party and its Subsidiaries and Sublicensees with their obligations under Section 4.2(b) or 4.3, as the case may be. Such audit shall be conducted upon at least ten (10) days' advance notice during normal business hours and in a manner that does not interfere unreasonably with the business of the audited entity. Any underpayment or overpayment determined by such audit shall promptly be paid or refunded by Hybridon or Isis, as the case may be. If a Party has underpaid an amount due under Section 4.2(b) or 4.3, as the case may be, by more than five percent (5%), such Party shall also reimburse the other Party for the cost of such audit (with the cost of the audit to be paid by the other Party in all other cases).

Section 4.5 PAYMENT CURRENCY. All amounts due under this Agreement shall be paid to the designated Party in United States currency by wire transfer to an account in a United States bank specified by such Party or in such other form and/or manner as such Party may reasonably request. The payments due on sales in currencies other than United States dollars shall be calculated using the appropriate exchange rate of such currency quoted in the Wall Street Journal on the close of business on the last business day prior to which such payment is made.

Section 4.6 LATE PAYMENTS; COLLECTIONS. Any amount not paid when due under this Agreement or the Master Agreement shall bear interest at the lesser

of (i) one and one-half percent (1.5%) per month, compounded monthly, or (ii) the highest rate permitted by law. Each Party agrees to pay all costs of collection, including reasonable attorneys' fees, incurred by the other Party in enforcing the payment obligations of the first Party under this Agreement and the Master Agreement.

ARTICLE V
COLLABORATION

In addition to the collaboration between the Parties with respect to intellectual property protection under Article VI, the Parties shall further collaborate hereunder through a committee (the "Collaboration Committee") consisting of two representatives of each Party. The Parties shall establish the Collaboration Committee within thirty (30) days after the Effective Date. The Collaboration Committee shall meet at least twice each calendar year in person or by video conference during the term of this Agreement to review the progress of Isis' development efforts with respect to Isis' Antisense Products that are covered by Hybridon Intellectual Property. The Parties intend that the Collaboration Committee shall act as a forum for the Parties to work cooperatively [*] The Parties also anticipate that the Collaboration Committee may recommend to the Parties from time to time that certain aspects of the drug development process be performed by Hybridon for Isis or that the Parties consider entering into further collaborations. Neither Party shall be bound by any recommendation of the Collaboration Committee but shall consider its recommendations in good faith. In addition, neither Party shall be obligated to disclose any Confidential Information to the Collaboration Committee.

ARTICLE VI
INTELLECTUAL PROPERTY PROTECTION

Section 6.1 Patent Prosecution and Cooperation.

(a) PROSECUTION AND MAINTENANCE OF HYBRIDON ANTISENSE PATENT RIGHTS.

(i) Hybridon will be responsible for prosecuting and maintaining the Hybridon Antisense Patent Rights. Hybridon shall promptly forward to Isis' patent counsel any substantive actions prepared for or received from the U.S. Patent and Trademark Office or any foreign patent office which may materially affect patent rights, e.g., claim scope or patent term. Isis' patent counsel shall provide any comments to Hybridon in sufficient time for Hybridon to reflect such comments in any response. Any comments made by Isis shall be made in good faith and shall be directed to maximizing the claims covered by the Hybridon Antisense Patent Rights.

(ii) If Hybridon agrees with the comments of Isis' patent counsel, it shall reflect such comments in its response. If Hybridon

disagrees with such comments, it shall notify Isis, and either Party may then submit such dispute (a "Patent Comment Dispute") for resolution by an intellectual property lawyer (the "Neutral Lawyer") with at least five years of experience and a background in biotechnology or pharmaceutical patent matters. The Neutral Lawyer shall be selected by mutual agreement of the Parties; provided, however, that if the Parties

cannot agree on a Neutral Lawyer within five days of a Party's request for a Neutral Lawyer under this provision, the Neutral Lawyer shall be selected by the American Arbitration Association in Washington, D.C. Each Party shall submit its position as to the Patent Comment Dispute to the Neutral Lawyer, who shall resolve the dispute by agreeing to one of the submitted positions of the Parties without any changes to such position. The Parties agree that the position agreed to by the Neutral Lawyer shall be reflected in the action or response being prepared and that the costs of the Neutral Lawyer shall be paid by the Party whose position is not agreed to by the Neutral Lawyer. The decision of the Neutral Lawyer shall be final and binding on the Parties. In light of the foregoing dispute resolution mechanism, neither Party shall submit a Patent Comment Dispute to binding arbitration in accordance with the provisions of Article VIII. The Parties shall cooperate in all respects to resolve any Patent Comment Dispute in sufficient time to avoid any loss of rights, including without limitation jointly instructing the Neutral Lawyer to make a decision in sufficient time to avoid any loss of rights.

(iii) Isis will be responsible for and pay fifty percent (50%) of Hybridon's costs incurred in prosecuting and maintaining the Hybridon Antisense Patent Rights, net of amounts paid to Hybridon for such costs by other licensees and not including any costs of Hybridon incurred in connection with a Patent Comment Dispute (except as otherwise specified in the foregoing Section 6.1(a)(ii)). Hybridon shall direct its counsel to invoice Isis directly for Isis' share of such costs as such costs are incurred.

(b) JOINT PATENT COMMITTEE. Hybridon and Isis will, within sixty (60) days after the execution of this Agreement, establish a committee (the "Joint Patent Committee") consisting of three representatives of each Party. The Joint Patent Committee shall confer twice each calendar year or as necessary to support timely decision making during the term of this Agreement to discuss patent prosecution issues, budgets and strategies relating to the Hybridon Antisense Patent Rights. The Joint Patent Committee shall also, as set forth in Section 5.2(b), determine which Party faces the greatest competitive threat in the event of infringement by a third party of any of the Hybridon Antisense Patent Rights. In the event that the Joint Patent Committee is unable to resolve any matter presented for resolution,. either Party shall have the right to submit such matter to binding arbitration in accordance with the provisions of Article VIII.

(c) INTERFERENCE BETWEEN ISIS INTELLECTUAL PROPERTY AND HYBRIDON ANTISENSE PATENT RIGHTS. If an interference is declared between any of the Isis Intellectual Property and any of the Hybridon Antisense Patent Rights (other than the UMass Patent Rights), each Party shall be represented by its own counsel in the interference proceedings; provided, however, that Hybridon's counsel shall be jointly selected by Isis and

Hybridon; and provided further that if Hybridon and Isis can not agree on counsel for Hybridon, a patent lawyer with at least five years of experience in interference practice and a background in biotechnology or pharmaceutical patent matters shall be selected to represent Hybridon by the American Arbitration Association in Washington, D.C. Each Party shall

seek to resolve the interference in a manner that maximizes the value to both parties of the combined portfolio of the Hybridon Antisense Patent Rights and the Isis Intellectual Property. If an interference is declared between any UMass Patent Rights and any Isis Intellectual Property, Hybridon will cooperate with Isis in the resolution thereof to the extent permitted under the UMass Agreement or, if Hybridon cannot so cooperate due to obligations to UMass, Isis will not be obligated to reimburse Hybridon for any expenses related to the interference proceedings. If an interference is declared between any of the Hybridon Antisense Patent Rights and the intellectual property of a third party or between any of the Isis Intellectual Property and the intellectual property of a third party, then Hybridon or Isis, as the case may be, shall have sole control of prosecuting the interference.

(d) PATENT COOPERATION. Isis hereby represents and warrants as of the date hereof that since April 26, 2001, neither Isis nor any of its Affiliates has challenged, opposed or taken any action to provoke any interference with any Hybridon Intellectual Property, and Isis agrees that from and after the date of this Agreement Isis shall not, and shall cause its Non-Parent Affiliates to not, challenge, oppose or take any action to provoke any interference with, or maintain any current challenge or opposition to, any Hybridon Intellectual Property. Hybridon hereby represents and warrants as of the date hereof that since April 26, 2001, neither Hybridon nor any of its Affiliates has challenged, opposed or taken any action to provoke any interference with any Isis Intellectual Property, and Hybridon agrees that from and after the date of this Agreement Hybridon shall not, and shall cause its Non-Parent Affiliates to not, challenge, oppose or take any action to provoke any interference with, or maintain any current challenge or opposition to, any Isis Intellectual Property. Hybridon further agrees that it will not use any Hybridon Antisense Patent Rights to challenge or interfere with any patents owned by Isis arising out of inventions invented, licensed or sublicensed by Isis prior to April 26, 2001, including those included in the Isis Intellectual Property, and that Hybridon will not oppose any patents claiming inventions invented, licensed or sublicensed by Isis prior to April 26, 2001, including those included in the Isis Intellectual Property, that cover chemical modifications to antisense oligonucleotides. The foregoing obligations not to challenge, oppose or interfere include, without limitation obligations not to directly or indirectly provoke an interference, participate in an opposition or make any claims of invalidity; PROVIDED THAT either Party and its Affiliates may raise a claim

of invalidity as a defense in a lawsuit filed by the other Party or its Affiliates. In addition, in the context of any interference between any of the Isis Intellectual Property and any of the Hybridon Antisense Patent Rights provoked by the U.S. Patent and Trademark Office, the Parties shall use commercially reasonable efforts to reach a settlement that maximizes the value to both Parties of the combined portfolio of the Hybridon Antisense Patent Rights and the Isis Intellectual Property.

(e) Notwithstanding any provision of this Section 6.1 to the contrary, nothing in this Section 6.1 shall (x) prevent Hybridon from complying with its obligations with respect to the Hybridon Intellectual Property under the UMass Agreement or the Third Party License Agreements, as applicable, or (y) limit the rights of the third parties under such agreements with respect to the Hybridon Intellectual Property, including as to clauses (x) and (y):

(i) UMass' right to prepare, file, prosecute and maintain certain patents and patent applications in the name of UMass pursuant to Section 8.1 of the UMass Agreement;

(ii) Hybridon's obligation to use counsel acceptable to UMass and to consult with UMass regarding the preparation, filing, prosecution or maintenance of certain patents and patent applications pursuant to Section 8.1 of the UMass Agreement;

(iii) Hybridon's obligation pursuant to Section 8.2 of the UMass Agreement (A) to provide notice to UMass prior to abandoning, or failing to make payment or take other necessary actions to maintain, certain patents and patent applications and (B) to continue the prosecution or maintenance of such patents after notice has been provided and before UMass has had sufficient time to assume the prosecution or maintenance of such patent;

(iv) Methylgene's right under Section 5.5 of the Methylgene License Agreement to take measures to ensure the registration and

maintenance of certain patents and patent applications if Hybridon fails to register and maintain such patents and patent applications;

(v) Methylgene's right under Section 5.5 of the Methylgene License Agreement to (A) approve the patent agent selected to prosecute certain patents and patent applications, (B) be kept informed regarding progress or problems related to certain patents and patent applications and (C) have its comments on such progress or problems be considered;

(vi) OriGenix's right under Section 5.5 of the OriGenix License Agreement to take measures to ensure the registration and maintenance of certain patents and patent applications if Hybridon fails to register and maintain such patents and patent applications;

(vii) OriGenix's right under Section 5.5 of the OriGenix License Agreement to (A) approve the patent agent selected to prosecute certain patents and patent applications, (B) be kept informed regarding progress or problems related to certain patents and patent applications and (C) have its comments on such progress or problems be considered;

(viii) EpiGenesis' right pursuant to Section 6.2.2 of the Development and License Agreement between EpiGenesis Pharmaceuticals, Inc. and Hybridon, dated as August 9, 2000 (the "EpiGenesis License Agreement") to file, prosecute and maintain certain patents and patent applications if Hybridon elects not to continue to seek or maintain patent protection on such patents or patent applications;

(ix) EpiGenesis' right pursuant to Section 6.2.2 of the EpiGenesis License Agreement to (A) have Hybridon consult with EpiGenesis regarding the prosecution of certain patents and patent applications, (B) have a reasonable amount of time to consider and comment on any document to be filed in connection with the prosecution of such patents and patent applications and (c) have its comments on such comments be seriously considered;

(x) Hybridon's obligation pursuant to Section 6.2.3 of the EpiGenesis License Agreement (A) to provide notice to EpiGenesis prior to abandoning, or failing to make payment or take other necessary actions to maintain certain patents and patent applications and (B) to continue the prosecution or maintenance of such patents and patent applications after notice has been provided and before EpiGenesis has had sufficient time to assume the prosecution or maintenance of such patents and patent applications; and

(xi) Boston Biosystems, Inc.'s (BBI) right and Avecia Holdings plc's right to prosecute or maintain certain patents and patent applications if Hybridon declines to prosecute or maintain such patents or patent applications pursuant to (A) Section 4.03 of the PNT Monomer Patent License and Option Agreement dated as of September 20, 2000 by and between Hybridon and BBI, (B) Section 4.03 of the Oligonucleotide Purification Patent License Agreement

dated as of September 20, 2000 by and between Hybridon and BBI, and (C) Section 5.03 of the Interference Patent Sublicense Option Agreement dated as of September 20, 2000 by and between Hybridon and BBI.

Section 6.2 ENFORCEMENT OF HYBRIDON ANTISENSE PATENT RIGHTS

(a) NOTICE. If Hybridon or Isis becomes aware that any of the Hybridon Antisense Patent Rights is infringed by a third party or is subject to a declaratory judgment action relating to infringement or invalidity, Hybridon or Isis, as the case may be, shall promptly notify the other Party.

(b) FIRST RIGHT OF ENFORCEMENT. In the event of infringement of the Hybridon Antisense Patent Rights by a third party, the Party facing the greatest competitive threat from the infringement shall have the first right (but not the obligation), at its sole expense, to undertake such action as it shall determine, in its discretion, appropriate to enforce the Hybridon Antisense Patent Rights; provided, however, that such Party

shall not admit the invalidity or unenforceability of any Hybridon Antisense Patent Rights, grant a license to the allegedly infringing third party or enter into any settlement agreement without the other Party's prior written consent. The determination of which Party faces the greatest competitive threat from the infringement shall be made by the Joint Patent Committee. If the Joint Patent Committee determines that neither Party faces a greater competitive threat than the other Party, then Hybridon shall have the first right to enforce the Hybridon Antisense Patent Rights. The Party enforcing the Hybridon Antisense Patent Rights shall keep the other Party reasonably informed on a quarterly basis, in person or by telephone, prior to and during any such enforcement. The other Party shall assist the Party enforcing the Hybridon Antisense Patent Rights, upon the enforcing Party's request and at the enforcing Party's sole expense, in taking any action to enforce the Hybridon Antisense Patent Rights and shall join in any such action if deemed by a court of competent jurisdiction to be a necessary party. Neither Party shall incur liability to the other Party as a consequence of such litigation or any unfavorable decision resulting therefrom, including any decision holding any of the Hybridon Antisense Patent Rights invalid, not infringed or unenforceable. Notwithstanding the foregoing, if Isis is the Party enforcing the Hybridon Antisense Patent Rights under this Section 6.2(b) and such Hybridon Antisense Patent Rights are included in the claims that are the subject matter of the UMass Agreement or are licensed by Hybridon under the Third Party License Agreements, Isis' rights to enforce such Hybridon Antisense Patent Rights shall be limited to the rights of Hybridon to enforce such Hybridon Antisense Patent Rights, and subject to and limited by the rights of the other parties to the

UMass Agreement and the Third Party License Agreements, as set forth in the UMass Agreement or the Third Party License Agreements, as applicable, including:

(i) UMass's right pursuant to Section 9.2 of the UMass Agreement to prosecute any infringements of certain patents and patent applications licensed to Hybridon pursuant to the UMass Agreement;

(ii) Hybridon's obligation pursuant to Section 9.3 of the UMass Agreement to seek the consent of UMass to any settlement, consent judgement or other voluntary final disposition of a suit involving certain patents and patent applications licensed to Hybridon pursuant to the UMass License;

(iii) UMass' right to intervene and take over the sole defense of a declaratory judgment action pursuant to Section 9.6 of the UMass Agreement;

(iv) Methylgene's right pursuant to Section 5.1(b) of the Methylgene License Agreement to initiate infringement actions related to certain patents and patent applications as it may in its discretion deem necessary or desirable;

(v) OriGenix's right pursuant to Section 5.1(v) of the OriGenix License Agreement to initiate infringement actions related to certain patents and patent applications as it may in its discretion deem necessary or desirable; and

(vi) EpiGensesis' right pursuant to Section 6.6 of the EpiGenesis License Agreement to initiate infringement actions related to certain patents and patent applications and to consent to any settlement of infringement litigation that would materially diminish the rights of EpiGenesis in certain patents and patent applications.

Items (i) through (vi) of this Section 6.2(b) are collectively referred to as the "Other Enforcement Rights".

(c) ENFORCEMENT BY OTHER PARTY. If the Party having the first right to enforce the Hybridon Antisense Patent Rights pursuant to Section 5.2(b) above fails to file an action to abate an infringement of the Hybridon Antisense Patent Rights, within six (6) months after a written request from the other Party to do so, or if such Party fails to diligently prosecute or discontinues the prosecution of any such action, the other Party at its sole expense may, in its discretion, undertake such action as it determines appropriate (other than the grant of a license to the allegedly infringing third party) to enforce such Hybridon Antisense

Patent Rights. Such other Party shall keep the Party that had the first right to enforce the Hybridon Antisense Patent Rights reasonably informed on a quarterly basis, in person or by telephone, prior to and during any such enforcement. In such case, the Party that had the first right to enforce the Hybridon Antisense Patent Rights shall assist such other Party, upon such other Party's request and at such other Party's sole expense, in taking any action to enforce the Hybridon Antisense Patent Rights and shall join in any such action if deemed by a court of competent jurisdiction to be a necessary party. Neither Party shall incur liability to the other Party as a consequence of such litigation or any unfavorable decision resulting therefrom, including any decision holding any of the Hybridon Antisense Patent Rights invalid, not infringed or unenforceable. Notwithstanding the foregoing, if Isis is the Party enforcing the Hybridon Antisense Patent Rights under this Section 6.2(c) and such Hybridon Antisense Patent Rights are included in the claims that are the subject matter of the UMass Agreement or are licensed by Hybridon under the Third Party License Agreements, Isis' rights to enforce such Hybridon Antisense Patent Rights shall be limited to the rights of Hybridon to enforce such Hybridon Antisense Patent Rights, and subject to and limited by the rights of the other parties to the UMass Agreement and the Third Party License Agreements, as set forth in the UMass Agreement or the Third Party License Agreements, as applicable, including the Other Enforcement Rights.

(d) RECOVERIES. All monies recovered upon the final judgment or settlement of any action involving the enforcement of Hybridon Antisense Patent Rights as contemplated by this Section 6.2 shall be allocated in the following order of priority: (i) first to reimburse the costs and expenses (including reasonable attorney fees and costs) incurred by the Parties in prosecuting such action, and (ii) any remaining portion of the recovery shall be divided between the Parties in proportion to the respective total losses, determined by aggregating both past and prospective losses, each Party would have been reasonably likely to have suffered had such infringement continued unabated. Notwithstanding the foregoing, if the Hybridon Antisense Patent Rights that were the subject of the action are included in the claims that are the subject matter of the UMass Agreement or are licensed by Hybridon under the Third Party License Agreements, the provisions of this Section 6.2(d) shall only apply to such monies recovered upon the final judgment or settlement of such action as remain following payment of monies to third parties as required under the UMass Agreement and the Third Party License Agreements.

ARTICLE VII
CONFIDENTIALITY

Section 7.1 CONFIDENTIAL INFORMATION. Each Party agrees that all Confidential Information of a Party that is disclosed by a Party to the other

Party (a) shall be maintained in confidence by the receiving Party and shall not be used by the receiving Party for any purpose other than as permitted under this Agreement, and (b) shall not be disclosed by the receiving Party to any third party who is not a Subsidiary of the receiving Party, or a consultant or an advisor to the receiving Party or a Subsidiary of the receiving Party, without the prior written consent of the disclosing Party; provided, however, that Confidential Information may only be disclosed by the receiving Party to Subsidiaries or consultants or advisors to the receiving Party or its Subsidiaries if such Subsidiaries, consultants or advisors, as the case may be, have agreed in writing to be bound by the obligations of the receiving Party under this Section 7.1. Notwithstanding the foregoing, the receiving Party shall be entitled to use and disclose Confidential Information that:

(a) was known or used by the receiving Party or its Subsidiaries prior to its date of disclosure to the receiving Party as demonstrated by legally admissible evidence available to the receiving Party or its Subsidiaries; or

(b) either before or after the date of the disclosure to the receiving Party is lawfully disclosed to the receiving Party or its Subsidiaries by sources other than the disclosing Party rightfully in possession of the Confidential Information and not bound by confidentiality obligations to the disclosing Party or its Subsidiaries; or

(c) either before or after the date of the disclosure to the receiving Party is or becomes published or otherwise is or becomes part of the public domain through no breach hereof on the part of the receiving Party or its Subsidiaries; or

(d) is independently developed by or for the receiving Party or its Subsidiaries without reference to or reliance upon the Confidential Information as demonstrated by competent written records; or

(e) is reasonably necessary to conduct clinical trials or for regulatory approval of products or for the filing, prosecution and maintenance of patents and patent applications, PROVIDED THAT the receiving Party provides prior written notice of such disclosure to the disclosing Party and takes reasonable and lawful actions to avoid and/or minimize the degree of such disclosure; or

(f) is required to be disclosed by the receiving Party to comply with applicable laws, to defend or prosecute litigation or to comply with governmental regulations, PROVIDED THAT the receiving Party provides prior written notice of such disclosure to the disclosing Party

and takes reasonable and lawful actions to avoid and/or minimize the degree of such disclosure.

ARTICLE VIII
DISPUTE RESOLUTION

Section 8.1 Except as set forth in Section 6.1(a)(ii), each Party must submit any dispute under this Agreement or the Master Agreement to arbitration by notifying the other Party, in writing, of such dispute. Within 30 days after receipt of such notice, the Parties shall designate in writing one arbitrator to resolve the dispute; PROVIDED, that if the Parties cannot agree on an arbitrator within such 30 days period, the arbitrator shall be selected by the office of the American
Arbitration Association in the city where arbitration will take place. The arbitrator shall not be an employee, consultant, officer, director or stockholder of any Party or its Affiliates. If neither the Parties nor the applicable office of the American Arbitration Association is able to identify an individual to serve as the arbitrator, the American Arbitration Association shall select an arbitrator from the CPC Panel of Distinguished Neutrals of the CPR Institute for Dispute Resolution.

Section 8.2 Within 30 days after the designation of the arbitrator, the arbitrator and the Parties shall meet, at which time the Parties shall be required to set forth in writing all disputed issues and a proposed ruling on the merits of each such issue.

Section 8.3 The arbitrator shall set a date for a hearing, which shall be no later than 45 days after the submission of written proposals to discuss each of the issues identified by the Parties. Each Party shall have the right to be represented by counsel. Except as provided herein, the arbitration shall be governed by the Commercial Arbitration Rules of the American Arbitration Association; PROVIDED, HOWEVER, that the Federal Rules of Evidence shall apply with regard to the admissibility of evidence and the arbitration shall be conducted by a single arbitrator.

Section 8.4 The arbitrator shall use his or her best efforts to rule on each disputed issue within 30 days after the completion of the hearings. The determination of the arbitrator as to the resolution of any dispute shall be final and binding and conclusive upon all parties hereto. All determinations of the arbitrator shall be in writing and shall be delivered to the Parties. The determinations of the arbitrator may be entered in any court of competent jurisdiction.

Section 8.5 The attorneys' fees of the Parties in any arbitration, the fees of the arbitrator, and the costs and expenses of the arbitration (collectively, the "Arbitration Costs") shall be borne by the Parties as determined by the arbitrator.

Section 8.6 The arbitration shall take place in Boston, Massachusetts if brought by Isis and in San Diego, California if brought by Hybridon.

Section 8.7 Nothing in this Article VIII shall prevent either Party from seeking a preliminary injunction, temporary restraining order or similar relief in order to prevent or limit and irreparable harm that might occur in the absence thereof from a court of competent jurisdiction.

ARTICLE IX
TERM AND TERMINATION

Section 9.1 TERM. This Agreement shall commence as of the date hereof and shall continue until the last of the patents and patent applications included in the Hybridon Intellectual Property, the Isis Intellectual Property and the Tullis Patents has expired, subject to earlier termination of this Agreement in accordance with this Article IX. Notwithstanding the foregoing, the licenses or sublicenses granted hereunder shall terminate on a country-by-country basis concurrently with the expiration or termination of the applicable Valid Claim under the Hybridon Intellectual Property, the Isis Intellectual Property or the Tullis Patents, as the case may be, in the applicable country.

Section 9.2 TERMINATION OF LICENSES AND SUBLICENSES FOR BREACH.

(a) Except as set forth in Section 9.2(b), (i) if an arbitrator has rendered a ruling pursuant to Article VIII that a Party or a Subsidiary has materially breached this Agreement or the Master Agreement, which ruling specified the remedies imposed on such breaching party for such breach, including without limitation a ruling on a dispute as to breach of a Party's obligation to issue stock or pay cash in lieu of stock as required under the Master Agreement (the "ADVERSE RULING"), and (ii) the breaching Party has failed to comply with the terms of the Adverse Ruling within the time period specified therein for compliance, or if such compliance cannot be fully achieved by such date, the breaching Party has failed to commence compliance and to use diligent efforts to achieve full compliance as soon thereafter as is reasonably possible, then the non-breaching Party shall be entitled to terminate the licenses and sublicenses granted to the breaching Party and its Subsidiaries by such non-breaching Party under this Agreement (without prejudice to any of the other rights of the non-breaching Party under this Agreement or the Master Agreement) upon written notice to the breaching Party.

(b) (i) If a Party breaches an obligation to issue stock or pay cash in lieu of stock as required under the Master Agreement, then the non-breaching Party may terminate the licenses and sublicenses granted to the breaching Party and its Subsidiaries by such

non-breaching Party under this Agreement immediately upon written notice to the breaching Party if the breaching Party fails to cure such breach within ten (10) business days of written notice of such breach from the non-breaching Party; provided, however, that if the breaching Party believes that a bona fide dispute exists as to the amount of any payment, then the breaching Party may, not later than five business days following the notice of the breach, (i) provide the non-breaching Party with a written notice setting forth the nature of the dispute and the amount in dispute, (ii) at the same time, pay to the non-breaching Party the amount of the payment which is not in dispute and (iii) promptly submit the dispute to binding arbitration pursuant to Article VIII, in which case the non-payment of the disputed portion shall not be deemed a breach during the pendency of the arbitration.

(ii) If the final arbitration order or ruling issued in the arbitration proceeding resolves the dispute against the breaching Party and orders the breaching Party to pay all or part of the disputed portion to the non-breaching Party, then the arbitrator shall include in its award, in addition to such other remedies as it deems appropriate, the following against the breaching Party: (A) the Arbitration Costs, (B) [*] and (C) if the arbitrator finds that a cash payment was due, an amount equal to interest at the rate equal to the lower of 1.5% per month, compounded monthly, or the highest rate permitted by law on the amount of cash determined to have been due commencing on the due date determined by the arbitrator through the date of actual payment.

(c) The right of either Party to terminate the licenses and sublicenses granted by such Party under this Agreement pursuant to this Section 9.2 shall not be affected in any way by its waiver of, or failure to take action with respect to any previous default.

(d) If the licenses and sublicenses granted by Hybridon to Isis and its Subsidiaries under this Agreement are terminated by Hybridon pursuant to this Section 9.2, (i) Hybridon shall be entitled to retain the licenses granted to it and its Subsidiaries pursuant to Article III, subject to the payment obligations of Hybridon specified in the Master Agreement and in Article IV, and to continue to receive the stock of Isis issuable to it pursuant to Section 2.3 of the Master Agreement, and (ii) the provisions of Articles V and VI shall terminate in their entirety. If the licenses and sublicenses granted by Isis to Hybridon and its Subsidiaries under this Agreement are terminated by Isis pursuant to this

Section 9.2, Isis shall be entitled to retain the licenses granted to it and its Subsidiaries pursuant to Article II, subject to the payment obligations of Isis specified in the Master Agreement and in Article IV, and to continue to receive the stock of Hybridon issuable to it pursuant to Section 2.2 of the Master Agreement.

Section 9.3 TERMINATION OF SUBLICENSE OF TULLIS PATENTS. Hybridon shall have the right to terminate the sublicense granted to it and its Subsidiaries pursuant to Section 3.3 (and the related payment obligations under Section 4.2) for any reason or no reason at any time upon fifteen (15) days prior written notice to Isis.

Section 9.4 SURVIVAL. The expiration or termination of this Agreement for any reason shall not relieve the Parties of any obligation due and accruing, or for any liability as to any breach occurring, prior to such expiration or termination. In addition, the provisions of Section 4.4, Article VII, Article VIII, Section 9.4, Section 9.5, and Article X shall survive the expiration or termination of this Agreement.

Section 9.5 SUBLICENSE SURVIVAL.

(a) Notwithstanding the termination of this Agreement or any of the licenses or sublicenses granted hereunder pursuant to this Article IX, any sublicenses to Isis Intellectual Property and the Tullis Patents granted by Hybridon or its Subsidiaries pursuant to Section 3.2 or 3.3(b) hereof prior to such termination shall survive such termination. In such event, Isis shall have the right to receive directly from the Sublicensee any payments or other consideration otherwise payable to Hybridon or its Subsidiaries as the sublicensor under such sublicense, and to otherwise exercise all of the rights of Hybridon or its Subsidiaries as the sublicensor under such sublicense; provided however that Isis shall not assume, and shall not be responsible for, any representations, warranties or obligations of Hybridon or its Subsidiaries as the sublicensor to any Sublicensees other than the licenses under such sublicenses.

(b) Notwithstanding the termination of this Agreement or any of the licenses or sublicenses granted hereunder pursuant to this Article IX, any sublicenses of Hybridon Intellectual Property granted by Isis or its Subsidiaries pursuant to Section 2.2 hereof prior to such termination shall survive such termination. In such event, Hybridon shall have the right to receive directly from the Sublicensee any payments or other consideration otherwise payable to Isis or its Subsidiaries as the sublicensor, under such sublicense and to otherwise exercise all of the rights of Isis or its Subsidiaries as the sublicensor under such sublicense; provided however that Hybridon shall not assume, and shall not be responsible for, any representations, warranties or obligations of Isis or its Subsidiaries as the sublicensor to any Sublicensees other than the licenses under such sublicenses.

Section 9.6 FAILURE TO MAKE MASTER AGREEMENT DELIVERIES. Notwithstanding any provision in this Agreement to the contrary, including without limitation Article VIII, [*] Hybridon shall have the right, at its sole election, effective immediately upon written notice to Isis, [*]

ARTICLE X
MISCELLANEOUS PROVISIONS

Section 10.1 INDEMNIFICATION. Each Party (the "Indemnifying Party") agrees to defend the other Party and such other Party's Subsidiaries and their respective directors, officers, employees and agents (the "Indemnified Parties") at the Indemnifying Party's cost and expense, and shall indemnify and hold the Indemnified Parties harmless from and against any losses, costs, damages, fees or expenses arising out of any third party claim relating to (i) any breach by the Indemnifying Party of any of its representations, warranties or obligations

pursuant to this Agreement, (ii) provided that the third party is not an Affiliate of the Indemnified Parties, infringement of such third party's patents resulting from the exercise by the Indemnifying Party or a Subsidiary or a Sublicensee of the

rights granted by the Indemnified Parties to the Indemnifying Party hereunder or (iii) product liability resulting from use of a product made, sold or imported

by or for the Indemnifying Party or by or for a Subsidiary or a Sublicensee under the rights granted by the Indemnified Parties hereunder. In the event of any claim against the Indemnified Parties by any third party for which indemnification may be sought pursuant to this Agreement, the Indemnified Parties shall promptly notify the Indemnifying Party in writing of the claim; provided that the failure to promptly notify the Indemnifying Party of such claim shall not result in the loss of rights of indemnification hereunder except to the extent that the Indemnifying Party was materially prejudiced by such failure. The Indemnifying Party shall assume, at its sole expense, the defense of the claim and its settlement. The Indemnified Parties shall cooperate with the Indemnifying Party and may, at their option and expense, be represented in any such action or proceeding. The Indemnifying Party shall not be liable for any litigation costs or expenses incurred by the Indemnified Parties. In addition, the Indemnifying Party shall not be responsible for the indemnification of any Indemnified Party arising from any negligent or wrongful acts by such Indemnified Party, or as the result of any settlement or compromise by the Indemnified Parties without the Indemnifying Party's prior written consent. The Indemnifying Party may not settle or compromise any matter without the consent of the Indemnified Parties unless such settlement or compromise imposes no obligations on the Indemnified Parties and does not restrict the rights of the Indemnified Parties.

Section 10.2 GOVERNING LAW. This Agreement shall be construed and the respective rights of the Parties determined according to the laws of the State of Delaware (without regard to the conflict of law rules of any jurisdiction), except matters of the intellectual property law, which shall be determined in accordance with the national intellectual property laws relevant of the intellectual property in question.

Section 10.3 ASSIGNMENT. Neither Hybridon nor Isis may assign this Agreement in whole or in part without the consent of the other Party, except if such assignment occurs in connection with the sale or transfer of all or substantially all of the business or assets of the assigning Party to which the subject matters of this Agreement pertains.

Section 10.4 ENTIRE AGREEMENT; AMENDMENTS. This Agreement, together with the Master Agreement, constitutes the entire agreement between the Parties with respect to the subject matter hereof, and supersedes all previous arrangements with respect to the subject matter hereof, whether written or oral. Any amendment or modification to this Agreement shall be made in writing signed by both Parties.

Section 10.5 NOTICES.

Notices to Hybridon shall be addressed to:

Hybridon, Inc.
345 Vassar Street
Cambridge, Massachusetts 02139
Attention: Chief Executive Officer

with a copy to:

Holland and Knight, LLP
10 St. James Avenue
Boston, Massachusetts 02116
Attention: James Pollock, Esq.

And

Hale and Dorr LLP
60 State Street
Boston, MA 02109
Attention: David E. Redlick, Esq.

Notices to Isis shall be addressed to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, California 92008
Attention: Chief Executive Officer
Copy to: Executive Vice President

Any Party may change its address by giving notice to the other Party in the manner herein provided. Any notice required or provided for by the terms of

this Agreement shall be in writing and shall be (a) delivered personally, (b) sent by registered or certified mail, return receipt requested, postage prepaid, (c) sent via a reputable overnight courier service, or (d) sent by facsimile transmission with an original to be followed the same day via a reputable overnight courier service, in each case properly addressed in accordance with the paragraph above. The effective date of notice shall be the actual date of receipt by the Party receiving the same.

Section 10.6 FORCE MAJEURE. No failure or omission by a Party in the performance of any of its obligations of this Agreement shall be deemed a breach of this Agreement or create any liability if the same shall arise from any cause or causes beyond the control of such Party, including, but not limited to, the following: acts of God; acts or omissions of any government; any rules, regulations or orders issued by any governmental authority or by any officer, department, agency or instrumentality thereof; fire; storm; flood; earthquake; accident; war; rebellion; insurrection; riot; and invasion and provided that such failure or omission resulting from one of the above causes is cured as soon as is practicable after the occurrence of one or more of the above-mentioned causes.

Section 10.7 DISCLOSURE OF PROVISIONS OF AGREEMENT.

(a) Each Party agrees to hold as confidential the terms of this Agreement, except that (i) Hybridon may furnish a copy of this Agreement to UMass, Isis may furnish a copy of this Agreement to MBI (other than Exhibits containing information relating to patent applications of Hybridon) and each Party shall have the right to disclose the terms of this Agreement (other than the information on the Exhibits hereto relating to patent applications of Isis or Hybridon) to potential investors and other third parties in connection with financing activities and to potential collaborators, provided that any such third party has entered into a written obligation with the disclosing Party to treat such information and materials as confidential and to not use the information and materials for any purposes other than the evaluation of the potential

investment or collaboration and that the disclosing Party shall enforce against the third party recipient of such information and materials, for and on behalf of the other Party, such written obligation, and (ii) each Party may furnish a copy of this Agreement or disclose the terms of this Agreement if such is required to be disclosed by the receiving Party to comply with applicable laws, to defend or prosecute litigation or to comply with governmental regulations, PROVIDED THAT the receiving Party provides prior written notice of such disclosure to the disclosing Party and takes reasonable and lawful actions to avoid and/or minimize the degree of such disclosure. At the request of the other Party, the disclosing Party shall use commercially reasonable efforts to enforce such obligations against such third parties.

(b) Notwithstanding Section 10.7(a) to the contrary, either Party may include this Agreement, in any report, statement or other document filed by such Party with the United States Securities and Exchange Commission (the "SEC"). In such event, the disclosing Party shall use reasonable efforts to obtain, to the extent permitted by law, confidential treatment from the SEC of any trade secrets and commercial or financial information of a privileged or confidential nature, including without limitation all information on the Exhibits hereto relating to patent applications of Isis or Hybridon, and shall notify the other Party as to such efforts and all related communications with the SEC; provided that notwithstanding the foregoing no Party shall submit a confidentiality request or include this Agreement without the prior review and approval of the confidentiality request by the other Party, which review and approval shall not be unreasonably withheld or delayed.

Section 10.8 INDEPENDENT CONTRACTORS. It is understood and agreed that the relationship between the Parties hereunder is that of independent contractors and that nothing in this Agreement shall be construed as authorization for either Party to act as agent for the other.

Section 10.9 NO STRICT CONSTRUCTION. This Agreement has been prepared jointly and shall not be strictly construed against any Party.

Section 10.10 HEADINGS. The captions or headings of the Sections or other subdivisions hereof are inserted only as a matter of convenience or for reference and shall have no effect on the meaning of the provisions hereof.

Section 10.11 NO IMPLIED WAIVERS; RIGHTS CUMULATIVE. No failure on the part of either Party to exercise, and no delay in exercising, any right, power, remedy or privilege under this Agreement, or provided by statute or at law or in

equity or otherwise, shall impair, prejudice or constitute a waiver of any such right, power, remedy or privilege or be construed as a waiver of any breach of this Agreement or as an acquiescence therein, nor shall any single or partial

exercise of any such right, power, remedy or privilege preclude any other or further exercise thereof or the exercise of any other right, power, remedy or privilege. In particular, the Parties hereby agree that termination of the licenses or sublicenses granted under this Agreement as provided in Article IX shall not be the exclusive remedy of a Party in the event of a breach of this Agreement or the Master Agreement by the other Party and that the non-breaching Party shall be entitled to seek any and all other remedies to which the non-breaching Party may be entitled at law or in equity.

Section 10.12 SEVERABILITY. If any provision hereof should be held invalid, illegal or unenforceable in any respect in any jurisdiction, then, to the fullest extent permitted by law, (a) all other provisions hereof shall remain in full force and effect in such jurisdiction and shall be liberally construed in order to carry out the intentions of the Parties as nearly as may be possible and (b) such invalidity, illegality or unenforceability shall not affect the validity, legality or enforceability of such provision in any other jurisdiction.

Section 10.13 EXECUTION IN COUNTERPARTS. This Agreement may be executed in counterparts, each of which counterparts, when so executed and delivered, shall be deemed to be an original, and all of which counterparts, taken together, shall constitute one and the same instrument.

Section 10.14 NO CONSEQUENTIAL DAMAGES. NEITHER PARTY HERETO WILL BE LIABLE FOR SPECIAL, INCIDENTAL OR CONSEQUENTIAL DAMAGES ARISING OUT OF THIS AGREEMENT OR THE EXERCISE OF ITS RIGHTS HEREUNDER, REGARDLESS OF ANY NOTICE OF SUCH DAMAGES.

Section 10.15 PATENT VALIDITY. Notwithstanding anything in this Agreement to the contrary, neither Party represents and warrants or shall be deemed to have represented and warranted to the other Party that the Hybridon Intellectual Property (in the case of Hybridon) and the Isis Intellectual Property and the Tullis Patents (in the case of Isis) are valid or otherwise enforceable.

[Remainder of page intentionally omitted]

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

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

Name: B. Lynne Parshall

Title: Executive Vice President

HYBRIDON, INC.

By: /s/ Sudhir Agrawal

Name: Sudhir Agrawal

Title: President and CSO

/s/ Robert Andersen, CFO

EXHIBIT A

[*]

*Confidential Treatment Requested

EXHIBIT B1

[*]

*Confidential Treatment Requested

EXHIBIT B2

[*]

*Confidential Treatment Requested

EXHIBIT C

[*]

*Confidential Treatment Requested

EXHIBIT D

[*]

*Confidential Treatment Requested

EXHIBIT E

[*]

*Confidential Treatment Requested

EXHIBIT F

[*]

*Confidential Treatment Requested

EXHIBIT G

[*]

*Confidential Treatment Requested

EXHIBIT H-1

THIRD PARTY LICENSE AGREEMENTS

Methylgene

AMENDED AND RESTATED LICENSE AGREEMENT MADE EFFECTIVE AS OF JANUARY 4, 1996, AS AMENDED AND RESTATED ON SEPTEMBER 21, 2000.

Origenix

LICENSE AGREEMENT DATED AS OF JANUARY 22, 1999 BETWEEN HYBRIDON AND ORIGENIX.

Epigenesis

DEVELOPMENT AND LICENSE AGREEMENT BETWEEN EPIGENESIS PHARMACEUTICALS, INC. AND HYBRIDON, INC., DATED AS OF AUGUST 9, 2000.

Boston Biosystems, Inc. (BBI)

PNT MONOMER PATENT LICENSE AND OPTION AGREEMENT DATED AS OF SEPTEMBER 20, 2000 BY AND BETWEEN HYBRIDON AND BBI.

OLIGONUCLEOTIDE PURIFICATION PATENT LICENSE AGREEMENT DATED AS OF SEPTEMBER 20, 2000 BY AND BETWEEN HYBRIDON AND BBI.

INTERFERENCE PATENT SUBLICENSE OPTION AGREEMENT DATED AS OF SEPTEMBER 20, 2000 BY AND BETWEEN HYBRIDON AND BBI.

EXHIBIT H-2

OTHER LICENSE AGREEMENTS

UMass Agreement

LICENSE AGREEMENT DATED AS OF FEBRUARY 21, 1990 AND RESTATED AS OF SEPTEMBER 8, 1993 BY AND BETWEEN HYBRIDON AND UNIVERSITY OF MASSACHUSETTS MEDICAL CENTER (FORMERLY THE WORCESTER FOUNDATION FOR BIOMEDICAL RESEARCH, INC.)

IDT Agreement

Non-Exclusive License Agreement dated as of March 12, 1999 between Integrated DNA Technologies, Inc. and Hybridon

EXHIBIT I

[*]

*Confidential Treatment Requested

EXHIBIT J

UMASS AGREEMENT

Incorporated by reference to Exhibit 10.1 to Hybridon's Registration Statement on Form S-1 (File No. 33-99024)

*Confidential Treatment Requested

EXHIBIT K

[*]

*Confidential Treatment Requested

EXHIBIT L

[*]

*Confidential Treatment Requested

EXHIBIT M

[*]

*Confidential Treatment Requested

EXHIBIT N

TULLIS AGREEMENT

Incorporated by reference to Exhibit 10.1 to Isis's Quarterly Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the quarterly period ended September 30, 1992, on Form 10-Q (File No. 0-19125).

*Text Omitted and Filed Separately
Confidential Treatment Requested
Under 17 C.F.R. Sections 200.80(b)(4)
200.83 and 240.24b-2

COLLABORATIVE RESEARCH AND LICENSE AGREEMENT

This COLLABORATIVE RESEARCH AND LICENSE AGREEMENT (the "Agreement") is made as of July 9, 2001 (the "Effective Date"), by and between ISIS PHARMACEUTICALS, INC., a Delaware corporation ("Isis"), having a principal place of business at Carlsbad Research Center, 2292 Faraday Avenue, Carlsbad, California 92008 and PE CORPORATION (NY), a New York corporation, through the CELERA GENOMICS GROUP, ("Celera"), having a principal place of business at 45 West Gude Drive, Rockville, Maryland 20850. Celera and Isis may be referred to herein individually as a "Party" and collectively as the "Parties".

RECITALS

WHEREAS, Isis possesses proprietary technology and know-how related to anti-sense technologies; and

WHEREAS, Celera possesses proprietary technology and know-how related to genomics; and

WHEREAS, Celera and Isis desire collaborate to generate information on gene function for up to [*] novel targets.

NOW, THEREFORE, in consideration of the various promises and undertakings set forth herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties agree as follows:

ARTICLE 1

DEFINITIONS

1.1 "Affiliate" with respect to either Party, will mean any Person controlling, controlled by, or under common control with such Party. For the purposes of this Section 1.1 only, "control" will refer to (a) the possession, directly or indirectly, of the power to direct the management or policies of a Person, whether through the ownership of voting securities, by contract or otherwise, together with (b) the ownership, directly or indirectly, of at least fifty percent (50%) of the voting securities or other ownership interest of a Person. Notwithstanding the foregoing, [*]

1.2 "Agreement NPV" means the net present value of any agreement calculated pursuant to Section Article 6.3(d) or as determined by the JEC by unanimous recorded vote.

1.3 "Antisense Inhibitor" means an Oligonucleotide that is designed to inhibit protein synthesis at the nucleic acid level by specifically binding to the sequence of a selected messenger or viral ribonucleic acid by base-paring.

* Confidential Treatment Requested

1.4 "Celera Exclusive Collaboration Patents" means all Patent Rights comprising method of use, method of prevention, treatment or diagnosis of a disease or condition or other identification of gene function associated with a Celera Exclusive Target arising out of the collaboration and for which Collaboration Data is used in the prosecution, maintenance or defense of such Patent Rights. Celera Exclusive Collaboration Patents specifically includes Collaboration Patents to the extent they otherwise come under the definition of Celera Exclusive Collaboration Patents.

1.5 "Celera Exclusive Targets" means the Celera Gene Targets selected by Celera pursuant to Section 3.2 (c), or any fragment or allelic variant of such Celera Gene Target or degenerative sequence of the foregoing encoding the identical amino acid sequence.

1.6 "Celera Gene Availability Pool" means the Celera Gene Targets available for Celera to designate for exclusive use pursuant to Section 3.2(c). Once the Option Period has expired for a specific Celera Gene Target it will cease to be part of the Celera Gene Availability Pool.

1.7 "Celera Gene Target" means a Gene selected for High Throughput Gene Functionalization.

1.8 "Celera Licensed Patents" means (i) all Patent Rights that are Controlled by Celera prior to the selection of Celera Gene Target pursuant to Section 3.1 that claim inventions consisting of any Celera Gene Target or any fragment of such Celera Gene Target, and/or any nucleic acid sequence, protein, peptide or other composition of matter encoded thereby, including, without limitation, inventions claiming method of use or treatment of a disease or condition by inhibiting such gene or other identification of gene function, and (ii) all Patent Rights whether or not Controlled by Celera not arising out of the collaboration where Collaboration Data is used in the prosecution, maintenance or defense of such Patent Rights. Celera Licensed Patents will specifically exclude Collaboration Patents, Celera Exclusive Collaboration Patents, Joint Patents and any Patent Rights that are Controlled by Celera claiming solely diagnosis of a disease or condition.

1.9 "Celera Product" means any Gene Therapy Product, Protein Therapeutic Product, Small Molecule Therapeutic Product or Vaccine Product discovered by Celera alone or as part of a bona fide drug discovery collaboration that, but for the licenses granted herein, would infringe a Celera Exclusive Collaboration Patent.

1.10 "Collaboration Data" means any and all data created using an Antisense Inhibitor pursuant to the Research Plan, including without limitation, in Isis's HGTF system.

1.11 "Collaboration Patents" means all Patent Rights comprising method of use, method of prevention, treatment or diagnosis of a disease or condition or other identification of gene function associated with a Celera Gene Target arising out of the collaboration and for which Collaboration Data is included in or used in the prosecution,

maintenance or defense of such Patent Rights. Collaboration Patents specifically excludes Oligonucleotide Patents. Collaboration Patents specifically includes jointly invented Patent Rights to the extent that they otherwise come under the definition of Collaboration Patents, and any such jointly invented Patent Rights will not be Joint Patents.

1.12 "Common Product" means (i) any and all Licensed Products that are neither Isis Products nor Celera Products for a Celera Exclusive Target, and (ii) any and all License Products that are not Isis Products for a Celera Gene Target that is not a Celera Exclusive Target.

1.13 "Confidential Information" means a Party's confidential information, inventions, know-how, data and materials relating to the Research, or the Celera Gene Targets, Celera Exclusive Targets, Lead Oligos or Licensed Products, including without limitation research, technical, clinical development, manufacturing, marketing, financial personnel and other business information and plans, which, if disclosed in written, graphic or electronic form, is marked or otherwise designated as "confidential" or "proprietary" and, if disclosed orally, is summarized and designated as "confidential" or "proprietary" in a writing provided to the receiving Party not later than sixty (60) days after such disclosure. All information presented at the JRC, Intellectual Property Committee or JEC meetings will be rebuttably presumed to be Confidential Information, regardless of whether it would otherwise qualify as such pursuant to the preceding sentence.

1.14 "Control" means, with respect to an item of Information or an intellectual property right, possession of the ability, whether by ownership or license, to grant a license or sublicense as provided for herein under such item or right without violating the terms of any agreement or other arrangements with any Third Party.

1.15 "Effective Date" means the effective date of this Agreement as set forth in the first paragraph above.

1.16 "Extended Term" has the meaning set forth in Section 5.1(e).

1.17 "Gene" means a DNA or RNA sequences of human or other origin that encodes a protein or other molecule.

1.18 "Gene Therapy Product" means any nucleic acid molecule, other than an Antisense Inhibitor or Oligonucleotide, that is introduced into human cells for the treatment or prevention of any disease, condition or risk based on modifying the expression of the target gene or modifying the genetic code of the target gene.

1.19 "High Throughput Gene Functionalization" or "HTGF" means Isis's High Throughput Screening system and standard phenotypic assays as it may exist from time-to-time and as more fully described in the Research Plan.

1.20 "Information" means any data, results, information, know-how, techniques, methods, development, material, or compositions of matter of any type or kind.

1.21 "Intellectual Property Committee" has the meaning set forth in Section 6.2.

1.22 "Isis Product" means any Oligonucleotide used in the treatment or prevention of a disease or condition that, but for the licenses granted herein, would infringe a Collaboration Patent.

1.23 "Joint Executive Committee" or "JEC" means that committee to be formed pursuant to Section 6.3.

1.24 "Joint Patents" means all Patent Rights that claim inventions that are made by employees or agents of Celera and Isis jointly and name as inventors one or more employees of Celera and Isis together with one or more employees or agents of the other Party. Joint Patents will not include any Collaboration Patents or Oligonucleotide Patents.

1.25 "Joint Research Committee" or "JRC" means that committee to be formed pursuant to Section 6.1.

1.26 "Lead Oligo" means an Antisense Inhibitor to a Celera Gene Target which decreases expression of such Celera Gene Target by at least [*].

1.27 "Lead Oligo Reagent" means a Lead Oligo derived using the 2'-methoxyethyl gapmer with fully phosphorothioate backbone chemistry of the HTGF system or an alternative for certain limited applications.

1.28 "Licensed Product" means any composition, material, device, kit, process or other product or process, the manufacture, use or sale of which would infringe a Collaboration Patent.

1.29 "Licensing Revenue" means revenue derived from the licensing of Collaboration Patents to Third Parties including without limitation, license fees, maintenance fees, milestones, and royalties but excluding payments for research and development. If either Party licenses Collaboration Patents to Third Parties together with other material intellectual property, the consideration received for such license, will be allocated by such Party in good faith among the components of the license. If payments are made in non-cash consideration, such Party will, at its option, either provide the other Party consideration in kind or in cash (based on a reasonable determination of value).

1.30 "Minimum Permitted Value" means a net present value of an agreement equal to [*].

1.31 "Oligonucleotide" means any compound containing between [*] nucleotides and/or nucleosides, including oligonucleotide analogs which may include natural or modified heterocycles, sugars and or backbone linkages.

1.32 "Oligonucleotide Patent" means all Patent Rights arising out of the collaboration that claims Antisense Inhibitors or Oligonucleotides and/or their method of use including without limitation the prevention or treatment of a disease or condition.

*Confidential Treatment Requested 4

Oligonucleotide Patents will include any jointly invented Patent Rights that otherwise meets this definition.

1.33 "Option" has the meaning set forth in Section 3.2(c).

1.34 "Option Period" has the meaning set forth in Section 3.2(c).

1.35 "Patent Right" means (i) an issued and existing patent, including any extensions, supplemental protection certificates, registrations, confirmations, reissues, reexaminations or renewals thereof, (ii) pending applications, including any continuation, divisional, or continuation-in-part application thereof, for any of the foregoing, and (iii) all counterparts to any of the foregoing issued by or filed in any country or other jurisdiction.

1.36 "Person" means any natural person, corporation, firm, business trust, business unit, joint venture, association, organization, company, limited liability company, partnership or other business entity, or any

government or agency or political subdivision thereof.

1.37 "Protein Therapeutic Product" means a protein, peptide or peptidomimetic analogous to a peptide or any derivative of the foregoing that is used for the treatment or prevention of any disease, condition or risk thereof.

1.38 "Research" means the collaborative research program undertaken by the Parties pursuant to the Research Plan during the Research Term.

1.39 "Research Plan" means the specific plan for HTGF screening of Celera Gene Targets, as described in Section 2.1, which will be attached hereto as Exhibit A.

1.40 "Research Term" means the period commencing on the Effective Date and terminating eighteen (18) months thereafter (or such earlier date as of which this Agreement is terminated hereunder).

1.41 "Small Molecule Therapeutic Product" means a small organic or inorganic molecule (less than 800 daltons) used for the treatment or prevention of any disease, condition or risk thereof, excluding any such molecule whose primary mode of activity is binding to RNA.

1.42 "Sublicensee" means a Person other than an Affiliate of Isis or Celera to which Isis or Celera has granted sublicense rights under the licenses granted hereunder, which rights include at least the rights to make and sell Licensed Products.

1.43 "Third Party" means any Person other than Celera, Isis or Affiliates of either of them, or any Sublicensee.

1.44 "Vaccine Product" means a protein, peptide or a nucleic acid molecule other than an Oligonucleotide, that stimulates an active specific immune response for the treatment or prevention of a disease or condition.

1.45 "Valid Claim" means a claim of an issued and unexpired patent which has not been revoked or held unenforceable or invalid by a decision of a court or governmental agency of competent jurisdiction from which no appeal can be taken or, after mutual consultation and agreement, an appeal is not taken within the time allowed for appeal, and which has not been disclaimed, denied or admitted to be invalid or unenforceable through reissue or disclaimer or otherwise.

ARTICLE 2

RESEARCH

2.1 Subject to the terms and conditions herein, the Parties will each use commercially reasonable diligent efforts to conduct the Research on a collaborative basis. Subject to Section 2.2(d) and other applicable provisions, the Parties will conduct the Research as specified in the Research Plan. The Research Plan attached hereto as Exhibit A describes the HTGF screening process that will be used to create Antisense Inhibitors to Celera Gene Targets and screen such Antisense Inhibitors in Isis' phenotypic assays to provide information useful in gene functionalization and target validation.

2.2 Conduct of the Research.

(a) The Research will be managed and directed by the JRC, as provided in 6.1.

(b) During the course of the Research, each Party will disclose to the other such Information as the other Party reasonably needs to conduct its obligations and assigned tasks under the Research Plan.

(c) In order to protect the Parties' patent rights in any inventions conceived or reduced to practice during or as a result of the Research, each Party agrees to implement a policy which requires its employees to record and maintain all data and information developed during the Research in such a manner as to enable the Parties to use such records to establish the earliest date of invention and/or diligence to reduction to practice.

(d) The Parties agree to commit the quality and quantity of resources required to perform their obligations under the Research Plan.

2.3 Liability. In connection with the conduct of the Research, each Party will be responsible for, and hereby assumes, any and all risks of

personal injury or property damage attributable to the negligent acts or omissions of that Party and its directors, officers, employees and agents.

ARTICLE 3

SELECTION OF CELERA GENE TARGETS AND CELERA EXCLUSIVE TARGETS

3.1 Selection of Celera Gene Targets.

(a) Celera will select Genes for functionalization studies under the Research Plan ("Celera Gene Targets") and notify Isis of the identity of such Celera Gene Target in writing.

(b) Genes selected by Celera under Section 3.1(a) will be included in the HTGF queue unless prior to such selection: (i) such Genes were prioritized by Isis for the HTGF queue; (ii) Isis had generated Antisense Inhibitors to such Gene; or (iii) Isis has bona fide pre-existing agreement to work on such Gene with a Third Party (Subsections (i), (ii) and (iii), "Rejected Genes"); and provided that Isis notifies Celera of the identity of any Rejected Gene in writing within ten (10) business days of Celera's selection of such Gene. Celera may select a replacement Gene for any Rejected Gene and such Rejected Gene will be treated as if it had never been selected by Celera. The identity of any Celera Gene Target or Rejected Gene will be the Confidential Information of Celera.

(c) Isis agrees to conduct the Research under the Research Plan and will provide reports to the JRC on a quarterly basis. These reports will contain all information necessary to keep the JRC fully informed regarding the performance of the Research Plan. Notwithstanding the preceding sentence, the Parties acknowledge that there is no guarantee that a Lead Oligo will be discovered using the HTS process.

(d) Celera knows and understands that it will be the primary source of Celera Gene Targets under the Research Plan and that Isis will not conduct any patent due diligence regarding its freedom to synthesize or screen Antisense Inhibitors to such targets or to provide Antisense Inhibitors to Celera hereunder. Subject to Sections 10.1 and 10.3, Celera will indemnify and hold Isis harmless from any liability to Third Parties by reason of the use by Isis of Celera Gene Targets solely for Isis' work under the Research Plan during the Research Term. For clarification, Celera will not indemnify Isis, and Celera will not be liable to Isis for any use of Celera Gene Targets after Isis is notified to cease use of any Celera Gene Target, any use of Celera Gene Targets in any Isis database, any use of Celera Gene Targets outside the Research Plan, or any use of Celera Gene Targets in the development and/or commercialization of Common Products or Isis Products.

3.2 Selection of Celera Exclusive Targets.

(a) Isis will perform the work described in the Research Plan and deliver any resulting data to the JRC and the Intellectual Property Committee in a timely fashion ("Collaboration Data"). Such Collaboration Data will include the assay and phenotype data as set forth in the Research Plan.

(b) Promptly after receiving the Collaboration Data with regard to a Celera Gene Target, the JRC and the Intellectual Property Committee will review the Collaboration Data. Upon delivery of the Collaboration Data, such Celera Gene Target will become part of a pool of Celera Gene Targets available to Celera for its use in accordance with the terms of this Agreement (the "Celera Gene Availability Pool"). If Isis informs the JRC that it is unable to create an optimized Antisense Inhibitor to such

Celera Gene Target and, as a result, will not be delivering Collaboration Data to the JRC for such Celera Gene Target, such Celera Gene Target will not be included in the Celera Gene Availability Pool.

(c) Celera will have the option, on a rolling basis, to designate up to [*] Celera Gene Targets from the Celera Gene Availability Pool, together with the Collaboration Data for such Celera Gene Targets, for Celera's exclusive use ("Celera Exclusive Targets") for Celera Products pursuant to Section 4.3(a) (the "Option"). For any given Celera Gene Target, Celera will exercise such Option, if at all, by giving written notice to Isis during a period commencing on the date that the JRC determines that no further work will be done on such Celera Gene Target and Isis delivers the Collaboration Data as outlined in the Research Plan for such target to the JRC

and ending [*] (the "Option Period"). Celera may replace any Celera Exclusive Target with any Celera Gene Target in the Celera Gene Availability Pool provided (i) the number of Celera Exclusive Targets does not [*] and (ii) the Option Period for any such Celera Gene Target has not expired. For clarification, only Celera Gene Targets in the Celera Gene Availability Pool will be subject to the Option. If Celera does not exercise its Option for any given Celera Gene Target during the applicable Option Period, or if Celera notifies Isis in writing that it will not exercise its Option for such Celera Gene Target, such Celera Gene Target will be deemed excluded from the Celera Gene Availability Pool. After any such exclusion, such Celera Gene Target will cease to be a Celera Gene Target, and Celera may not exercise its Option with regard thereto.

ARTICLE 4

LICENSES AND OTHER RIGHTS

4.1 Licenses to Conduct the Research. Subject to the other provisions of this Agreement, Celera hereby grants to Isis during the Research Term a nonexclusive worldwide, paid up right and license, without the right to sublicense, under the Celera Licensed Patents solely to conduct the Research.

4.2 Isis Database. Isis will have the right to commercialize the Collaboration Data in a database format unless such Collaboration Data (i) is subject to Celera's Option during the Option Period pursuant to Section 3.2, or (ii) contains or comprises in whole or in part any Collaboration Data for a Celera Exclusive Target. Notwithstanding the foregoing, Celera may provide Isis, upon Isis's written request, with written approval to use any Collaboration Data in a database format, which would be otherwise restricted from use under the first sentence of this Section. Isis will inform its subscribers regarding the Collaboration Data added to the Isis Database pursuant to this Section 4.2 that Collaboration Patents, if any, associated with such data are subject to the licensing requirements set forth in Section 4.3.

4.3 Use of the Joint Patents, Collaboration Patents and Other Data. Both Parties will have the right to practice the Joint Patents and the Collaboration Patents and use the Collaboration Data and the data provided by a Party to the other Party pursuant to Section 5.1(c), for internal research purposes; provided however,

(a) Isis hereby grants Celera an exclusive right and license (including with regard to Isis), with the right to sublicense and without obligation to Isis, under Isis's rights in the Joint Patents and the Celera Exclusive Collaboration Patents, to conduct development on, and to make, have made, import, use, sell and have sold Celera Products;

(b) Celera hereby grants Isis an exclusive right and license (including with regard to Celera), with the right to sublicense and without obligation to Celera, under Celera's rights in the Joint Patents and the Collaboration Patents, to conduct development on, and to make, have made, import, use, sell and have sold Isis Products; and

(c) Both Parties will have the right and license, without obligation of notice or payment to the other Party, to conduct development on, and to make, import, use, sell and offer for sale Common Products with the limited right to sublicense solely for development and commercialization.

(d) Celera will have the exclusive right and license (including with regard to Isis), to grant sublicenses to make, import, use, sell and offer for sale Common Products under the Celera Exclusive Collaboration Patents (subject to the provisions of Section 7.2 regarding Revenue Sharing). Isis will have the exclusive right and license (including with regard to Celera), to grant sublicenses to make, import, use, sell, and offer for sale Common Products under the Joint Patents and the Collaboration Patents except the Celera Exclusive Collaboration Patents (subject to the provisions of Section 1.63 regarding Revenue Sharing).

4.4 License to Celera Licensed Patents. Celera hereby grants Isis a nonexclusive right and license, without the right to sublicense except in connection with the sublicense of an Isis Product discovered by Isis alone or as part of a bona fide drug discovery collaboration, under Celera's rights in the Celera Licensed Patents, to conduct development on, and to make, have made, import, use, sell and have sold Isis Products. Notwithstanding the foregoing, if Isis is unable to generate a Lead Oligo to a Celera Gene Target pursuant to the Research Plan, any and all Patent Rights that claim such Celera Gene Target will be excluded from the license set forth in the preceding sentence.

4.5 Negative Covenants.

(a) Isis covenants to Celera that Isis will not research, develop or commercialize or license any Third Party or an Affiliate to research, develop or commercialize any Celera Product claimed by Celera Exclusive Collaboration Patents.

(b) Celera covenants to Isis that:

(i) Celera will not research, develop or commercialize, or license any Third Party or an Affiliate to research, develop or commercialize any Isis Product claimed by Collaboration Patents; and

(ii) Celera will not enter into any agreement with any Third Party whose core business includes the provision of Antisense Inhibitors for gene functionalization during the Research Term.

4.6 Limited Rights. Nothing in this Agreement is intended or will be interpreted as granting to Isis or any Third Party any right or interest in any Patent Rights, Information, trade secrets, copyrights, trademarks, trade names or other intellectual property rights (a) invented, discovered, developed, or otherwise created by PE Corporation (NY), or its Affiliates, other than by the Celera Genomics Group, or (b) acquired or licensed by PE Corporation (NY), or its Affiliates, other than solely for the benefit of the Celera Genomics Group.

ARTICLE 5

OTHER SERVICES

5.1 Supply of Antisense Inhibitors.

(a) Isis will provide Lead Oligo Reagent to each Celera Exclusive Target and to [*] Celera Gene Targets that are not Celera Exclusive Targets claimed by Celera Licensed Patents as provided in Section 4.4, at a rate of [*] per order for up to [*] of a Lead Oligo, for Celera's internal research and development of Celera Products and/or Common Products as applicable ("Other Services"). Celera may request and Isis may agree to negotiate commercially reasonable terms for the provision to Celera of additional Lead Oligo Reagent to other Celera Gene Targets.

(b) Except as otherwise provided under this Agreement, all such Antisense Inhibitors delivered to Celera will be used only in furtherance of the Research, will not be used or delivered to or for the benefit of any Third Party without the prior written consent of Isis, and will not be used in research or testing involving human subjects. The Antisense Inhibitors supplied under this Section 5.1 must be used with prudence and appropriate caution in any experimental work, since not all of their characteristics may be known.

(c) THE ANTISENSE INHIBITORS BEING PROVIDED TO CELERA HEREUNDER ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

(d) Celera agrees that it will not, nor will it request any Third Party, to synthesize Antisense Inhibitors to any Celera Gene Target during the Research Term or for the longer of [*] thereafter or (ii) such time as the discovery, manufacture, use or sale of such Antisense Inhibitors would no longer infringe a Valid Claim of a Patent Right Controlled by Isis.

(e) Antisense Inhibitors discovered under the Research Plan are identified using patented technology.

(i) During the Research Term and for [*] thereafter (the "Extended Term"), if Celera derives any Information from research not under the Research Plan using Lead Oligo Reagent provided by Isis to Celera pursuant to Section 5.1(a), Celera will promptly provide such Information to Isis. Notwithstanding the obligation to provide such Information, Celera hereby grants Isis an exclusive right and license (including with regard to Celera), without the right to sublicense, except in connection with the sublicense of an Isis Product discovered by Isis alone or as part of a bona fide drug discovery collaboration, and without obligation to Celera, under Celera's rights in any Patents Rights in which information derived using such Lead Oligo Reagent during and after the Extended Term is used in the filing prosecution,

maintenance or defense of such Patent Rights, to conduct development on, and to make, have made, import, use, sell and have sold Isis Products.

(ii) During the Extended Term, if Isis derives any Information from research not under the Research Plan on Celera Exclusive Targets using Antisense Inhibitors identified under the Research Plan, and/or on Celera Gene Targets that are claimed by Celera Licensed Patent Rights as provided in Section 4.4, Isis will promptly provide all data derived from such research to Celera, excluding data derived from any use in humans. Notwithstanding the obligation to provide such Information, Isis hereby grants Celera a non-exclusive right and license, without the right to sublicense, except in connection with the sublicense of a Celera Product discovered by Celera alone or as part of a bona fide drug discovery collaboration, and without obligation to Isis, under any Patent Rights claiming all Information derived from such research during and after the Extended Term, to conduct development on, and to make, have made, import, use, sell and have sold Celera Products.

5.2 Custom Target Validation. Celera will have an option to identify up to [*] Celera Gene Targets for custom target validation. Custom target validation may include pharmacology studies of effects of antisense inhibitor in additional cell-based or animal models. Terms and conditions for custom target validation will be negotiated in good faith but no less than Isis' fully-burdened cost plus appropriate milestones and royalties.

ARTICLE 6

MANAGEMENT OF THE COLLABORATION

6.1 Creation and Structure of the Joint Research Committee.

(a) Within ten (10) business days of the Effective Date, the Parties will create a Joint Research Committee of two (2) persons to facilitate the research collaboration called for herein. The JRC will consist one (1) representative nominated by each Party. Members of the JRC may be represented at any meeting by a designee appointed by such member for such meeting. Each Party will be free to change its representatives on notice to the other or to send a substitute representative of equal qualification and authority to any JRC meeting.

(b) The JRC will meet as necessary but no less frequently than every three (3) months during the Research Term. Meetings will be via teleconference or videoconference. At its first meeting the JRC will determine such procedures as it will reasonably require to conduct its business.

(c) During the Research Term, the JRC will be the primary vehicle for interaction between the Parties with respect to the Research. Without limiting the foregoing, the JRC will be responsible for (i) determining for each Celera Gene Target whether to proceed to conduct Secondary Assays as described in the Research Plan. (ii) reviewing and commenting upon the patent filing strategies of the Collaboration Patents, the Celera Exclusive Collaboration Patents and the Joint Patent Rights as provided in Article 8; (iii) reviewing and commenting upon publications as contemplated by Section 9.2; and (iv) managing the activities of the Intellectual Property Committee. The items in Subsections (ii) and (iii) will be delegated to the Intellectual Property Committee.

(d) All decisions of the JRC will be made by the unanimous vote of the members. If the members of the JRC cannot agree with respect to a particular issue such issue will be referred to the JEC which will make a reasonable good faith effort to reach agreement thereon within a ten (10) business day period after such issue is presented to the JEC in writing.

6.2 Creation and Structure of the Intellectual Property Committee.

(a) At the first meeting of the JRC, the JRC will create an Intellectual Property Committee. The Intellectual Property Committee will be managed and directed by the JRC. The Intellectual Property Committee will be composed of the two (2) JRC members plus two (2) additional members, one from each of Isis and Celera.

(b) The roles of the Intellectual Property Committee will be (i) to conduct the IP mining described in the Research Plan, (ii) to review and approve any publications containing Collaboration Data except inclusion of Collaboration Data in the Isis database as anticipated by this Agreement, and (iii) to manage the prosecution, defense and maintenance of the Collaboration Patents and the Joint Patents.

(c) The Intellectual Property Committee will meet as needed either in person, by teleconference or via videoconference. At the first meeting of the Intellectual Property Committee, the Committee will adopt such roles and procedures as it may deem necessary or appropriate to conduct their business.

(d) All decisions of the Intellectual Property Committee will be made by the unanimous vote of the members, if the members of the Intellectual Property Committee cannot agree with respect to a particular issue such issue will be referred to the JEC which will make a reasonable good faith effort to reach agreement thereon within ten (10) business days after such issue is presented to the JEC in writing.

(e) The Intellectual Property Committee will continue in effect after the termination of this Agreement for so long as Collaboration Patents or Joint Patents are

being prosecuted and maintained, or such shorter time as mutually agreed to by the Parties in writing.

6.3 Creation and Structure of the Joint Executive Committee.

(a) Within ten (10) business days of the Effective Date, the Parties will create a Joint Executive Committee of two (2) people, one from each Party to oversee the research collaboration and commercialization activities called for herein. The JEC will be composed of one (1) representative appointed by each of Celera and Isis. Either Party may replace one (1) its representative at any time upon written notice to the other Party with a person of equal authority and expertise.

(b) The JEC will exist for so long as the JRC or Intellectual Property Committee is in existence or either Party has the right to conduct commercialization activities pursuant to Section 4.3(d). The JEC will meet as requested by the JRC or Intellectual Property Committee. On matters requiring the approval of the JEC, such approval will be by the unanimous vote of all JEC members participating in the meeting. In the event the JEC is unable to reach agreement on all issues, it will be resolved in accordance with Section 12.11. The JEC will meet within thirty (30) days of the Effective Date and thereafter as needed or at the request of either Party to carry out the function set forth in this Section 6.3.

(c) The JEC will be the primary vehicle for oversight of the research collaboration activities. Without limiting the foregoing, the JEC will be responsible for (i) review and resolution of any material deviation from the Research Plan; and (ii) review and resolution of any dispute elevated to it by the JRC or the Intellectual Property Committee.

(d) Through the JEC the Parties will keep each other reasonably informed on an ongoing basis of the substantive terms of any proposed agreement to grant sublicenses pursuant to Section Article 4.3(d).

(i) [*]

(ii) [*]

ARTICLE 7

PAYMENTS AND REVENUE SHARING

7.1 Research Funding.

(a) Celera will pay Isis [*] to conduct the Research under the Research Plan. Celera will pay Isis [*] of the Effective Date. Notwithstanding the foregoing, if Isis fails in a material way to conduct the Research according to the Research Plan Celera may withhold payment of the following [*] until such material failure is remedied, whereupon such [*] will be paid in full or in such fraction as the Parties shall reasonably agree. Any

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dispute with regard to such payment withholding will be promptly elevated to dispute resolution pursuant to Section 12.11(a).

(b) Delivery schedule and funding for Other Services described in Article 5 will be agreed upon and paid in advance in the amounts agreed to by the Parties.

7.2 [*].

7.3 Mode of Payment and Reports. All payments to hereunder will be made to the receiving Party within sixty (60) days of the end of the quarter in which the receiving Party receives the payment by deposit of United States Dollars in the requisite amount to such bank account as the receiving Party may from time-to-time designate by notice to the paying Party. The paying Party will provide to the receiving Party with each such payment a report in sufficient detail to show the basis for such payment.

7.4 Audits.

(a) Upon the written request of the receiving Party and not more than once in each calendar year, the paying Party will permit an independent certified public accounting firm of nationally recognized standing selected by the paying Party, and reasonably acceptable to the receiving Party at the receiving Party's expense, to have access during normal business hours, and upon reasonable prior written notice, to such of the records of the paying Party as may be reasonably necessary to verify the accuracy of the reports under Section 7.3 for the prior calendar year only. The accounting firm will disclose to the Parties only whether the reports are correct or incorrect and the specific details concerning any discrepancies. No other information will be provided to Celera.

(b) If such accounting firm concludes that additional payments were owed during such period, the paying Party will pay the additional payments, with interest from the date originally due at the prime rate, as published in The Wall Street Journal (Eastern U.S. Edition) on the last business day preceding such date, within thirty (30) days after the date the receiving Party delivers to the paying Party such accounting firm's written report. [*]

(c) For any sublicense granted by either Party hereunder which triggers payments to the other Party pursuant to this Article 7, the grantor of such sublicense will include in each sublicense granted by it pursuant to this Agreement a provision requiring the Sublicensee to keep and maintain records of sales made, pursuant to such sublicense and to grant access to such records by the licensing Party's independent accountant to the same extent required by such grantor under this Agreement.

(d) Celera and Isis will treat all information subject to review under this Section 7.4 or under any sublicense agreement in accordance with the confidentiality provisions of Article 9 of this Agreement.

7.5 Taxes. If any taxes are required to be withheld by the licensing Party, it will (a) deduct such taxes from the remitting payment, (b) timely pay the taxes to the proper

taxing authority, and (c) send proof of payment to the receiving Party and certify its receipt by the taxing authority within sixty (60) days following such payment.

ARTICLE 8

INVENTIONS AND PATENTS

8.1 Title to Inventions.

(a) Any Patent Rights covering inventions by the Parties during the Collaboration that do not constitute Collaboration Patents will be owned exclusively by the inventing party, subject to Subsection 8.1(c).

(b) Joint Patents will be jointly owned, subject to Subsection 8.1(c).

(c) Any inventions constituting Oligonucleotide Patents will be solely owned and assigned to Isis. Inventions with an antisense component and a broader compound will be broken into separate patent applications with the antisense-related inventions filed separately as Oligonucleotide Patents.

(d) Any inventions constituting Celera Exclusive Collaboration Patents will be solely owned and assigned to Celera (subject to the licenses granted to Isis hereunder).

(e) Inventorship will be determined by the applicable laws of the country or jurisdiction in which the particular Patent Right is sought.

(f) In the event that there is a dispute between the Parties as

to ownership under this Section, the Intellectual Property Committee will establish a procedure to resolve such dispute, which may include engaging a Third Party patent attorney completely unaffiliated and independent of the Parties and jointly selected by the Parties, as an expert to resolve such dispute.

8.2 Patent Prosecution.

(a) The Parties expect that patent applications will be filed and maintained as required to secure the Collaboration Patent Rights. Celera, with reasonable and timely input from Isis, will be responsible for filing, prosecuting and/or maintaining the Celera Exclusive Collaboration Patents throughout the world. Isis with reasonable and timely input from Celera, will be responsible for filing, prosecuting and/or maintaining the Collaboration Patents other than Celera Exclusive Collaboration Patents throughout the world. Celera and Isis will share equally the costs of filing, prosecuting and/or maintaining such Patent Rights. Notwithstanding the above, either Party may decline to pay its share of the costs for filing, prosecuting and/or maintaining any Collaboration

Patent(s) (a "Declining Party"), in which case such Declining Party will notify the other Party promptly in writing and in good time to enable the other Party to meet any applicable deadlines, and the other Party will have the right, but not the obligation, to undertake the responsibility for filing, prosecuting and/or maintaining such Collaboration Patents at its own expense, and the Declining Party will reasonably cooperate with and assist the other Party therein. A Declining Party will maintain its license under such Collaboration Patent pursuant to Article 4, except that any right to grant sublicenses therein (other than the sublicensing rights set forth in Sections 4.3(a) 4.3(b)), and any right to receive Licensing Revenue pursuant to Section 7.2 under such Collaboration Patents, will terminate as of the date a Declining Party provides such written notice. Such terminated sublicense rights shall be granted to the other Party, provided such other Party has exercised its right of filing, prosecuting and/or maintaining such Collaboration Patents.

(b) The Parties anticipate that there may be Joint Patents that arise out of the Collaboration (that do not constitute Collaboration Patents or Oligonucleotide Patents). To the extent that such a Joint Patent represents an improvement of one Party's technology and not the other, the Party whose technology is improved will have the sole right and responsibility, at its own expense, to prosecute and maintain such Joint Patent. To the extent that such a Joint Patent either represents an improvement to both Party's technology or does not improve either Party's technology, the Intellectual Property Committee will determine which of the Parties will be responsible for prosecution, maintenance, enforcement and defense of such Patent and what procedures will be put in place for coordination among the Parties including, without limitation, cost-sharing and input.

(c) Isis will be solely responsible, at its own expense, for prosecution, maintenance, defense and enforcement of any Oligonucleotide Patents.

8.3 Enforcement of Patents.

(a) If either Party considers that any Collaboration Patent is being infringed by a Third Party, it will notify the other Party and provide it with any evidence of such infringement which is reasonably available. Subject to any limitations in the license agreements between Celera or Isis and Third Party licensors covering licensed Patent Rights, the JEC will determine the steps to take to attempt to remove such infringement by commercially appropriate steps, including filing an infringement suit or taking other similar action.

(b) The Party not enforcing the applicable Patent Rights will provide reasonable assistance to the other Party, including providing access to relevant documents and other evidence and making its employees available, subject to the enforcing Party's reimbursement of any out-of-pocket expenses incurred by the non-enforcing Party.

(c) Any amounts recovered by a Party pursuant to Section 8.3(a) whether by settlement or judgment, will be allocated in the following order: (i) to reimburse Isis and Celera for their reasonable out-of-pocket expenses in making such

recovery (which amounts will be allocated pro rats if insufficient to cover the totality of such expenses); and (ii) the remainder will be allocated as the Parties will reasonably agree based upon damages suffered.

(d) Except for Third Party infringement activities covered by the provisions of Section (j) each Party will retain the sole and exclusive right to enforce its Patent Rights against all infringers at its sole cost and expense.

ARTICLE 9

CONFIDENTIALITY

9.1 Confidentiality Obligations. Each Party agrees that, for the term of this Agreement and for five (5) years thereafter, such Party will keep, and will ensure that its officers, directors, employees and agents keep, completely confidential and will not publish or otherwise disclose and will not use for any purpose except as permitted hereunder any Confidential Information furnished to it by the other Party pursuant to this Agreement (including, without limitation, Know-How of the disclosing Party). The foregoing obligations will not apply to any information to the extent that it can be established by such receiving Party that such information:

(a) was already known to the receiving Party as evidenced by its written records, other than under an obligation of confidentiality, at the time of disclosure;

(b) was generally available to the public or was otherwise part of the public domain at the time of its disclosure to the receiving Party;

(c) became generally available to the public or otherwise becomes part of the public domain after its disclosure and other than through any act or omission of the receiving Party in breach of this Agreement;

(d) was subsequently lawfully disclosed to the receiving Party by a Third Party other than in contravention of a confidentiality obligation of such Third Party to the disclosing Party; or

(e) was developed or discovered by employees of the receiving Party or its Affiliates who had no access to the Confidential Information of the disclosing Party. Each Party may disclose the other's Confidential Information to the extent such disclosure is reasonably necessary in filing or prosecuting patent applications, prosecuting or defending litigation, advising investors and the investment community of the results of the Research aid/or development activities hereunder (subject to reasonable prior written notice of, and good faith consultation about, such disclosure to the other Party), complying with applicable governmental regulations, making a permitted sublicense of its rights hereunder or otherwise in performing its obligations or exercising its rights hereunder, provided that if a Party is required to make any such disclosure of the other Party's Confidential Information, it will give reasonable advance notice to that other Party of such disclosure requirement, will cooperate with the other Party in its efforts to secure confidential treatment of such Information prior to its disclosure, and, save to the extent

inappropriate in the case of patent applications, will use all reasonable efforts to secure confidential treatment of such information prior to its disclosure (whether through protective orders or confidentiality agreement or otherwise).

9.2 Publications.

(a) The Collaboration Data will be the Confidential Information of Isis and Celera. Either Party may publish or present Collaboration Data subject to the prior review by the Intellectual Property Committee for patentability and protection of such other Party's Confidential Information. The Intellectual Property Committee will review any proposed abstracts, manuscripts or summaries of presentations which contain Collaboration Data. No publication or presentation containing Collaboration Data may be submitted or made without approval by the Intellectual Property Committee. The Intellectual Property Committee may delay any such approval to ensure protection of Patent Rights. Notwithstanding the foregoing, nothing contained herein will preclude Isis from including the Collaboration Data in its marketed database in accordance with the terms of this Agreement or presenting the Collaboration Data to Isis' potential customers for such database or in connection with either Parties active drug discovery programs, without approval of the Intellectual Property Committee.

(b) To the extent appropriate and within the Party's control, in any publication permitted under this Section 9.2, each Party will acknowledge its collaboration with the other Party under this Agreement

9.3 Press Releases. Except to the extent required by law or as otherwise permitted in accordance with this Section 9.3, neither Party will make any public announcements concerning this Agreement or the terms hereof without the prior written consent of the other, which will not be unreasonably withheld or delayed. Notwithstanding the foregoing, the Parties will issue a joint press release promptly following execution of this Agreement announcing (i) the execution of this Agreement; (ii) Celera and Isis will jointly identify novel gene function utilizing Celera's expertise in genomics and Isis' expertise in antisense technology; (iii) Celera will retain exclusive rights to a limited number of genes for the research and development of certain therapeutic products; and (iv) that functional information on [*] of these genes will be incorporated into Isis' Gene Function Database, and agree that each Party may desire or be required to issue subsequent press releases relating to the Agreement or activities thereunder, and the Parties agree to consult with each other reasonably and in good faith with respect to the text and timing of such press releases prior to the issuance thereof, provided that a Party may not unreasonably withhold consent to such releases, and that either Party may issue such press releases as it determines, based on advice of counsel, are reasonably necessary to comply with laws or regulations or for appropriate market disclosure.

ARTICLE 10

INDEMNIFICATION

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10.1 Indemnification by Celera. Celera will indemnify, defend and hold Isis and its agents, employees, officers and directors (the "Isis Indemnitees") harmless from and against any and all liability, damage, loss, cost or expense (including reasonable attorneys' fees) arising out of Third Party claims or suits related to (a) Celera's performance of its obligations under this Agreement; or (b) breach by Celera of its representations and warranties set forth in Section 12.3 or (c) Isis' use of Celera Gene Targets under the Research Plan pursuant to Section 3.1(d); PROVIDED, HOWEVER, that Celera's obligations pursuant to this Section 10.1 will not apply to the extent such claims or suits result from the gross negligence or willful misconduct of any of the Isis Indemnitees. Notwithstanding the foregoing, Celera will have no obligation to indemnify the Isis Indemnitees with respect to claims arising out of breach by Isis of its representations and warranties set forth in Sections 12.3.

10.2 Indemnification by Isis. Isis will indemnify, defend and hold Celera and its Affiliates and each of their respective agents, employees, officers and directors (the "Isis Indemnitees") harmless from and against any and all liability, damage, loss, cost or expense (including reasonable attorney's fees) arising out of Third Party claims or suits related to (a) Isis's performance of its obligations under this Agreement; or (b) breach by Isis of its representations and warranties set forth in Sections 12.3; provided however, that Isis's obligations pursuant to this Section 10.2 will not apply to the extent that such claims or suits result from the gross negligence or willful misconduct of any of the Celera Indemnitees. Notwithstanding the foregoing, Celera will have no obligation to indemnify the Celera Indemnitees with respect to claims arising out of a breach by Celera of its representations and warranties set forth in Section 12.3.

10.3 Notification of Claims. Conditions to Indemnification Obligations. As a condition to a Party's right to receive indemnification under this Article 10 it will (i) promptly notify the other Party as soon as it becomes aware of a claim or action for which indemnification may be sought pursuant hereto, (ii) cooperate with the indemnifying Party in the defense of such claim or suit, and (iii) permit the indemnifying Party to control the defense of such claim or suit, including without limitation the right to select defense counsel. In no event, however, may the indemnifying Party compromise or settle any claim or suit in a manner which admits fault or negligence on the part of the indemnified Party without the prior written consent of the indemnified Party. The indemnifying Party will have no liability under this Article 10 with respect to claims or suits settled or compromised without its prior written consent.

ARTICLE 11

TERMINATION AND EXPIRATION

11.1 Term and Termination. This Agreement will commence upon the Effective Date and, unless earlier terminated as provided herein, will expire

on the expiration of all royalty and other payment obligations herein.

11.2 Termination upon Material Breach. Failure by a Party to comply with any of its material obligations contained herein will entitle the Party not in default to give to

the Party in default notice specifying the nature of the default, requiring it to make good or otherwise cure such default, and stating its intention to terminate if such default is not cured. If such default is not cured within ninety (90) days after the receipt of such notice (or, if such default cannot be cured within such ninety (90) day period, if the Party in default does not commence and diligently continue actions to cure such default), the Party not in default will be entitled, without prejudice to any of its other rights conferred on it by this Agreement, and in addition to any other remedies available to it by law or in equity, to terminate this Agreement; PROVIDED HOWEVER, that such right to terminate will be stayed in the event that, during such ninety (90) day period, the Party alleged to have been in default will have initiated dispute resolution in accordance with Section 12.11 with respect to the alleged default, which stay will last so long as the initiating Party diligently and in good faith cooperates in the prompt resolution of such dispute resolution proceedings.

11.3 Consequences of Termination.

(a) Upon termination of this Agreement (but not upon expiration of its term under Section 11.1);

(i) each Party will promptly return all relevant records and materials in its possession or control containing or comprising the other Party's Confidential Information and to which the former Party does not retain rights hereunder (except one copy of which may be retained in a Party's confidential files in its legal department for archival purposes); and

(ii) all licenses granted under Sections 4.1, 4.1(a) and 4.3(d) will terminate; provided however, that all sublicenses previously granted will survive termination. All licenses granted under Section 4.2 and 4.3 will survive termination.

(b) The right of a Party to terminate this Agreement, as herein above provided, will not be affected in any way by its waiver or failure to take action with respect to any prior default.

11.4 Accrued Rights; Surviving Obligations.

(a) Termination, relinquishment or expiration of this Agreement for any reason will be without prejudice to any rights which will have accrued to the benefit of a Party prior to such termination, or expiration. Such termination, relinquishment or expiration will not relieve a Party from obligations which are expressly indicated to survive termination or expiration of this Agreement.

(b) Without limiting the foregoing, Sections 2.3, 3.1(d), 4.3(a), 4.3(b), 4.3(c), 4.5, 4.6, 7.3, 7.4, 7.5, 8.1, 8.2, 9.1, 11.3, 11.4 and 11.5 and Articles 10 and 12 of this Agreement will survive the expiration or termination of this Agreement for any reason.

11.5 Rights in Bankruptcy. All rights and licenses granted under or pursuant to this Agreement by Isis or Celera are, and will otherwise be deemed to be, for purposes of

Section 365(n) of the U.S. Bankruptcy Code, licenses of right to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code. The Parties agree that the Parties, as licensees of such rights under this Agreement, will retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding-by or against either Party under the U.S. Bankruptcy Code, the Party hereto which is not a party to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, and same, if not already in their possession, will be promptly delivered to them (i) upon any such commencement of a bankruptcy proceeding upon their written request therefor, unless the Party subject to such proceeding elects to continue to perform all of its obligations under this Agreement, or (ii) if not delivered under (i) above, following the rejection of this Agreement by or on behalf of the Party subject to such proceeding upon

written request therefor by the non-subject Party.

ARTICLE 12

MISCELLANEOUS PROVISIONS

12.1 Relationship of the Parties. Nothing in this Agreement is intended or will be deemed to constitute a partnership, agency or employer-employee relationship between the Parties. Neither Party will incur any debts or make any commitments for the other.

12.2 Assignments. Neither this Agreement nor any interest hereunder will be assignable, nor any other obligation delegable, by a Party without the prior written consent of the other Party; provided however, that either Party may assign this Agreement without consent to any successor in interest by way of merger or sale of all or substantially all of its assets in a manner such that the assignor will remain liable and responsible for the performance and observance of all of the assigning Party's duties and obligations hereunder, except that no intellectual property of any Third Party acquirer of Celera or Isis will be included in the licenses granted hereunder. This Agreement will be binding upon the successors and permitted assigns of the Parties. Any assignment not in accordance with this Section 12.2 will be void.

12.3 Representations and Warranties. Each Party represents and warrants to the other Party that, as of the date of this Agreement:

(a) Such Party is duly organized and validly existing under the laws of the state of its incorporation and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

(b) Such Party has taken all corporate action necessary to authorize the execution and delivery of this Agreement and the performance its obligations under this Agreement;

(c) This Agreement is a legal and valid obligation of such Party, binding upon such Party and enforceable against such Party in accordance with the terms of this Agreement The execution, delivery and performance of this Agreement by such

Party does not conflict with any agreement, instrument or understanding, oral or written, to which such Party is a party or by which such Party may be bound, and does not violate any law or regulation of any court, governmental body or administrative or other agency having authority over such Party. All consents, approvals and authorizations from all governmental authorities or other Third Parties required to be obtained by such Party in connection with this Agreement have been obtained

(d) It has the full and exclusive right, power and authority to enter into this Agreement, to perform the Research and to grant the licenses granted under Article 4;

(e) There are no agreements between such Party and any Third Parties which would preclude or otherwise limit such Party's ability to conduct its tasks and obligations under the Research Plan or otherwise fulfill its obligations under this Agreement;

(f) All individuals who will perform any activities on its behalf in connection with the Research have assigned to it or its Affiliates the whole of their rights in any intellectual property conceived or reduced to practice by them as a result of the Research, and no Third Party will have any rights to any such intellectual property.

12.4 Disclaimer of Warranties. THE PARTIES EXPRESSLY DISCLAIM ALL WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT OF THIRD PARTY RIGHTS, UNLESS OTHERWISE EXPRESSLY PROVIDED IN THIS AGREEMENT.

12.5 Further Actions. Each Party agrees to execute, acknowledge and deliver such further instruments and to do all such other acts as may be necessary or appropriate in order to carry out the purposes and intent of this Agreement.

12.6 Force Majeure. Neither Party will be liable to the other for failure or delay in the performance of any of its obligations under this Agreement for the time and to the extent such failure or delay is caused by earthquake, riot, civil commotion, war, strike, flood, governmental acts or restrictions or any other reason which is beyond the control of the respective Party. The Party affected by force majeure will provide the other Party with

full particulars thereof as soon as it becomes aware of the same (including its best estimate of the likely extent and duration of the interference with its activities), and will use commercially reasonable efforts to overcome the difficulties created thereby and to resume performance of its obligations as soon as practicable. If the performance of any obligation under this Agreement is delayed owing to a force majeure for any continuous period of more than six (6) months, the Parties hereto will consult with respect to an equitable solution, including the possibility of the mutual termination of this Agreement.

12.7 No Trademark Rights. Except as expressly set forth herein, no right, express or implied, is granted by this Agreement to a Party to use in any manner the name or any other trade name or trademark of a Party in connection with the performance of this Agreement.

12.8 Entire Agreement of the Parties; Amendments. This Agreement and the exhibits hereto constitute and contain the entire understanding and agreement of the Parties respecting the subject matter hereof and cancel and supersede any and all prior negotiations, correspondence, understandings and agreements between the Parties, whether oral or written, regarding such subject matter. No waiver, modification or amendment of any provision of this Agreement will be valid or effective unless made in writing and signed by a duly authorized officer of each Party.

12.9 Captions. The captions to this Agreement are for convenience only, and are to be of no force or effect in construing or interpreting any of the provisions of this Agreement

12.10 Applicable Law. This Agreement will be governed by and interpreted in accordance with the laws of the State of Delaware, USA, applicable to contracts entered into and to be performed wholly within the State of Delaware, excluding conflict of law principles.

12.11 Disputes. In the event of any controversy or claim arising out of, relating to or in connection with any provision of this Agreement or the rights or obligations of the Parties hereunder, the Parties will try to settle their differences amicably between themselves as contemplated herein. To the extent not provided for herein, either Party may initiate such informal dispute resolution by sending written notice of the dispute to the other Party, and within ten (10) days after such notice.

(a) The Chief Business Officer of Celera and the President of GeneTrove of Isis will meet for discussion and resolution. If such personnel are unable to resolve such dispute within thirty (30) days of initiating such negotiations, the Parties agree to settle any unresolved controversy or claim arising out of, relating to or in connection with this Agreement (except as to any issue relating to the ownership of intellectual property of either Party) in Dallas, Texas by binding arbitration under the American Arbitration Association in accordance with its Commercial Arbitration Rules as modified by this Section, and judgment upon the award rendered by the arbitrators may be entered in any court having jurisdiction thereof. Within fifteen (15) days after the commencement of arbitration, each Party will select one (1) person to act as arbitrator, and the two (2) selected by the Parties will select a third arbitrator within ten (10) days of their appointment. The Parties agree that in cases in which this Agreement explicitly provides that their disagreement will be settled by this Section, the arbitration method to be employed will be "baseball-style arbitration." This means that each Party will submit in writing to the Panel and the other Party at an appropriate time its final, detailed proposed resolution of the dispute. The panel will have the right to ask for and receive (at the same time as the other Party) clarification of a Party's proposed resolution. In its arbitration award, the panel will be limited to choosing, without material modification, one of the two proposed resolutions, together with an award of reasonable attorneys' fees to the prevailing Party. The arbitrators will have no authority to award punitive damages or any other damages not measured by the prevailing Party's actual damages, and may not, in any event, make any ruling, finding or award that does not conform to the terms and conditions of this Agreement. Neither Party nor the arbitrators may disclose the existence,

content, or results of any arbitration hereunder without the prior written consent of both Parties.

12.12 Notices and Deliveries. Any notice, request, delivery, approval or consent required or permitted to be given under this Agreement will be in writing and will be deemed to have been sufficiently given if delivered in

person, transmitted by facsimile (receipt verified) or by express courier service (signature required) or five (5) days after it was sent by registered letter, return receipt requested (or its equivalent), to the Party to which it is directed at its address or facsimile number shown below or such other address or facsimile number as such Party will have last given by notice to the other Party.

If to Isis, addressed to:

Isis Pharmaceuticals, Inc.
2292 Faraday Drive
Carlsbad, California 92008
Attn: Richard Brown, B. Lynne Parshall
Cc: GeneTrove President

If to Celera, addressed to:

Celera Genomics
45 West Gude Drive
Rockville, Maryland
Attn: Peter Barrett, Ph.D.
Cc: Group Counsel, Legal Affairs

12.13 No Consequential Damages. IN NO EVENT WILL EITHER PARTY OR ANY OF ITS RESPECTIVE AFFILIATES BE LIABLE TO THE OTHER PARTY OR ANY OF ITS AFFILIATES FOR SPECIAL, INDIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES, WHETHER IN CONTRACT, WARRANTY, TORT, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, INCLUDING, BUT NOT LIMITED TO, LOSS OF PROFITS OR REVENUE, OR CLAIMS OF CUSTOMERS OF ANY OF THEM OR OTHER THIRD PARTIES FOR SUCH OR OTHER DAMAGES.

12.14 Non-Solicitation. During the Research Term, and for a period of one (1) year thereafter, neither Party will solicit, induce, encourage or attempt to induce or encourage any employee of the other Party to terminate his or her employment with such other Party or to breach any other obligation to such other Party.

12.15 Waiver. A waiver by either Party of any of the terms and conditions of this Agreement in any instance will not be deemed or construed to be a waiver of such term or condition for the future, or of any subsequent breach hereof. All rights, remedies, undertakings, obligations and agreements contained in this Agreement will be cumulative and none of them will be in limitation of any other remedy, right, undertaking, obligation or agreement of either Party.

12.16 Compliance with Law. Nothing in this Agreement will be deemed to permit a Party to export, re-export or otherwise transfer any Licensed Product sold under this Agreement without compliance with applicable laws.

12.17 Severability. When possible, each provision of this Agreement will be interpreted in such manner as to be effective and valid under applicable law, but if any provision of this Agreement is held to be prohibited by or invalid under applicable law, such provision will be ineffective only to the extent of such prohibition or invalidity, without invalidating the remainder of this Agreement. The Parties will make a good faith effort to replace the invalid or unenforceable provision with a valid one which in its economic effect is most consistent with the invalid or unenforceable provision.

12.18 Counterparts. This Agreement may be executed simultaneously in any number of counterparts, any one of which need not contain the signature of more than one Party but all such counterparts taken together will constitute one and the same agreement

IN WITNESS WHEREOF, the Parties have caused this Agreement to be executed by their respective duly authorized officers as of the day and year first above written, each copy of which will for all purposes be deemed to be an original.

ISIS PHARMACEUTICALS, INC.	PE CORPORATION
By: ---------- (signature)	By: ---------- (signature)
Name: B. Lynne Parshall	Name: Peter Barrett, Ph.D.
Title: Executive Vice President	Title: E.V.P. and Chief Business Officer

Date: Date:
---------- ----------

EXHIBIT A
RESEARCH PLAN

This Exhibit A to the Collaborative Research and License Agreement (the "Agreement") dated as of July 9, 2001 addresses the conduct of the Research. Capitalized terms will have the meanings set forth in the Agreement.

The generation of functional information on [*] Celera Target Genes will follow a multi-step process: prioritization of genes, generation and validation of lead antisense oligos, and bioassay readout in four therapeutic areas (cancer, angiogenesis, inflammation, and metabolic disease). After the Collaboration Data is reviewed by the Joint Research Committee and Intellectual Property Committee and appropriate patent applications filed, the information will be used to populate the Gene Trove Gene Function Database, excluding information on [*] Celera Exclusive Targets.

Isis will provide reports to the JRC on a quarterly basis or more frequently. These reports will contain all information necessary to keep the JRC fully informed regarding the performance of the research plan.

[*]

*Confidential Treatment Requested

EXHIBIT B

[*]

* Confidential Treatment Requested