

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-Q/A (Amendment No. 1)

(Mark One)

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
(State or other jurisdiction of
incorporations or organization)

33-0336973
(I.R.S. Employer Identification No.)

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

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

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

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

(1) Yes No

(2) Yes 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
(Class)

42,247,956 shares
(Outstanding at June 30, 2001)

Explanatory Note

This amendment to the Form 10-Q, for the quarterly period ended June 30, 2001, is being filed solely to amend Part II, Item 6, Exhibit 10.2.

PART II—OTHER INFORMATION

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

- a. Exhibits

MASTER AGREEMENT

RELATING TO THE CROSS LICENSE OF CERTAIN INTELLECTUAL PROPERTY
AND COLLABORATION
BY AND BETWEEN
HYBRIDON, INC.
a Delaware corporation

AND
ISIS PHARMACEUTICALS, INC.
a Delaware corporation

DATED AS OF MAY 24, 2001

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MASTER AGREEMENT

This Master Agreement (this "MASTER AGREEMENT") dated as of May 24, 2001, is entered into by and between Hybridon, Inc., a Delaware corporation with its principal place of business at Cambridge, Massachusetts ("HYBRIDON"), and Isis Pharmaceuticals, Inc., a Delaware corporation with its principal place of business at Carlsbad, California ("ISIS").

WITNESSETH:

WHEREAS, each of Hybridon and Isis owns or licenses intellectual property that it wishes to license to the other; and

WHEREAS, as partial consideration for such license of intellectual property, Hybridon and Isis each intends to issue shares of common stock to the other and Isis intends to pay Hybridon a cash payment contemporaneously with the execution of this Master Agreement; and

WHEREAS, each of the parties has expended significant efforts and resources in the research and development of antisense technology and the payments to be made under this Master Agreement to each party hereto will allow each party heretoto recoup such expenditures; and

WHEREAS, the parties hereto wish to enter into a binding agreement with respect to the specific transactions and agreements set forth in this Master Agreement; and

WHEREAS, each of the parties to this Master Agreement desires to make certain representations, warranties and agreements in connection with the transactions contemplated hereby and also to prescribe various conditions thereto.

NOW, THEREFORE, in consideration of the foregoing recitals, the provisions and the respective agreements hereinafter set forth, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties agree as follows:

ARTICLE 1

DEFINED TERMS

1.1 DEFINITIONS. Capitalized terms used herein and not otherwise defined shall have the meanings set forth below:

"AFFILIATE" means, 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 definition, "control" shall mean (a) in the case of corporate entities, direct or indirect ownership of fifty percent (50%) or more of the stock

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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.

"AVERAGE CLOSING PRICE" means the Closing Prices of either Isis Common Stock or Hybridon Common Stock, as the context requires, averaged over any number of trading days as specified in this Master Agreement.

"CHANGE IN CONTROL TRANSACTION" means (a) any sale or transfer of all or substantially all of the assets of a Party to another individual, corporation or entity ("Type A"), (b) any merger, consolidation, reorganization, share exchange or business combination of a Party into or with another corporation or entity, with the result that, upon conclusion of the transaction, the voting securities of such Party immediately prior thereto do not represent (either by remaining outstanding or by being converted into voting securities of the surviving entity) more than 40% of the combined voting power of the voting securities of the continuing or surviving corporation or entity of such consolidation, merger, reorganization, share exchange or business combination ("Type B"), (c) any direct or indirect acquisition of securities in which a "person" or "group" (as used in Rule 13d-1 of the Exchange Act) directly or indirectly acquires beneficial or record ownership of voting securities of a Party representing at least 60% of the outstanding voting securities of such Party ("Type C"), or (d) any event that results in the securities of a Party issued or issuable under SECTION 2.2 (including SECTION 2.2(c)) or SECTION 2.3 (including SECTION 2.3(c)), as the case may be, no longer being a class of securities registered with the Commission pursuant to Section 12 of the Exchange Act ("Type D").

"CLOSING PRICE" means the midpoint of the high and low sale price of a share of the Hybridon Common Stock or the Isis Common Stock, as applicable, on any given day as reported on the Stock Market on which such security is traded.

"COMMISSION" means the Securities and Exchange Commission.

"EFFECTIVE DATE" means the date on which this Master Agreement is executed by the Parties.

"EXCHANGE ACT" means the Securities Exchange Act of 1934, as amended.

"HYBRIDON COMMON STOCK" means the common stock, \$.001 par value per share, of Hybridon.

"HYBRIDON INTELLECTUAL PROPERTY" shall have the meaning set forth in the License Agreement.

"HYBRIDON MARKET PRICE" means the Market Price of Hybridon Common Stock.

"HYBRIDON MAXIMUM PRICE" means \$3 for the first Hybridon Tranche Period, \$4 for the second Hybridon Tranche Period and \$5 for the third Hybridon Tranche Period, each as may be adjusted from time to time pursuant to SECTION 11.1.

"HYBRIDON MINIMUM PRICE" means \$1, as may be adjusted from time to time pursuant to SECTION 11.1.

"HYBRIDON RESTRICTED STOCK" means all shares of Hybridon Common Stock issued to Isis pursuant to this Master Agreement and all shares of capital stock which may, from time to time, be issued in respect of any such shares of capital stock, including, without limitation, all shares issued as a stock dividend, as a result of a stock split or pursuant to any reorganization, recapitalization, merger, consolidation or similar event.

"HYBRIDON TRANCHE PAYMENT" means the stock issuance to be made by Hybridon to Isis with respect to a Hybridon Tranche Period or, if permitted, the cash to be paid by Hybridon to Isis in lieu of such stock issuance.

"HYBRIDON TRANCHE PAYMENT DATE" means, as to a Hybridon Tranche Period, the next business day following the last day of the Hybridon Tranche Period or, if prior to such day, the date on which the Hybridon Tranche Payment for such Hybridon Tranche Period becomes payable pursuant to SECTION 2.2(b).

"HYBRIDON TRANCHE PERIOD" means any one of the three successive twelve-month periods commencing on the Effective Date.

"ISIS COMMON STOCK" means the common stock, \$.001 par value per share, of Isis.

"ISIS INTELLECTUAL PROPERTY" shall have the meaning set forth in the License Agreement.

"ISIS MARKET PRICE" means the Market Price of the Isis Common Stock.

"ISIS MAXIMUM PRICE" means \$14 for the first Isis Tranche Period, \$20 for the second and third Isis Tranche Period, and \$26 for the fourth Isis Tranche Period, each as may be adjusted from time to time pursuant to SECTION 11.1.

"ISIS MINIMUM PRICE" means \$7, as may be adjusted from time to time pursuant to SECTION 11.1.

"ISIS RESTRICTED STOCK" means all shares of Isis Common Stock issued to Hybridon pursuant to this Master Agreement and all shares of capital stock which may, from time to time, be issued in respect of any such shares of capital stock, including, without limitation, all shares issued as a stock dividend, as a result of a stock split or pursuant to any reorganization, recapitalization, merger, consolidation or similar event.

"ISIS TRANCHE PAYMENT" means the stock issuance to be made by Isis to Hybridon with respect to an Isis Tranche Period or, if permitted, the cash to be paid by Isis to Hybridon in lieu of such stock issuance.

"ISIS TRANCHE PAYMENT DATE" means, as to a Isis Tranche Period, the next business day following the last day of the Isis Tranche Period or if prior to such day, the date on which the Isis Tranche Payment becomes payable pursuant to SECTION 2.3(b).

"ISIS TRANCHE PERIOD" means any one of the four successive six-month periods commencing on the Effective Date.

"LOST PROFITS" means the product of (i) the number of shares of stock that should have been (but were not) issued to the non-breaching Party (the "UNISSUED STOCK") on the date specified in this Master Agreement (the "REQUIRED ISSUANCE DATE") and (ii) the excess, if any, of (a) the highest Closing Price on any date during the period from and including the Required Issuance Date (or the trading day immediately preceding the Required Issuance Date if the required Issuance Date is not a trading day on the Stock Market on which the stock of the breaching Party trades) up to the date the Unissued Stock is actually issued to the non-breaching Party (the "ACTUAL ISSUANCE DATE"), over (b) the Closing Price on the Actual Issuance Date (or the trading day immediately preceding the Actual

Issuance Date if the Actual Issuance Date is not a trading day on the Stock Market on which the stock of the breaching Party trades). In the event that the breaching Party shall have distributed any dividends in cash, stock or other property on or after the Required Issuance Date and on or prior to the Actual Issuance Date, or fixed a record date for the determination of stockholders entitled to receive a distribution of any dividends in cash, stock or other property which record date occurs on or after the Required Issuance Date and on or prior to the Actual Issuance Date, then Lost Profits shall also include the total dividends in cash, stock or other property which the non-breaching Party would have been otherwise entitled to receive if the Unissued Stock had been issued to the non-breaching Party on the Required Issuance Date.

"MARKET PRICE" means the Average Closing Price of Isis Common Stock or Hybridon Common Stock, as the case may be, for the 20 trading days immediately preceding a specified date.

"PARTY" means Hybridon or Isis and "PARTIES" means Hybridon and Isis. As used in this Master Agreement, references to third parties do not include a Party or its Affiliates.

"PER SHARE TRANSACTION VALUE" means

(a) in the case of Type A Change in Control Transaction, the value, as determined in good faith by the board of directors of the Party whose assets are being sold, of the distributions which the holder of one share of Hybridon or Isis Common Stock, as the case may be, would be entitled to receive (including the dilutive effect of the Hybridon or Isis Common Stock to be issued under Section 2.2(b)(iv) or Section 2.3(b)(iv), as the case may be, and of all

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other shares of Hybridon or Isis Common Stock which may be issued upon the conversion or exercise of securities of Hybridon or Isis, as the case may be, the issuance of which would be dilutive in light of the amount that will be available for distribution upon liquidation) if the Party selling its assets were to be liquidated upon consummation of the Change in Control Transaction, PROVIDED, HOWEVER, that in determining Per Share Transaction Value under this subparagraph (a) no consideration shall be given to any earn-outs or any other future payments to be determined after the consummation of the Change in Control Transaction, except any payments of amounts held in escrow; or

(b) in the case of a Type B Change in Control Transaction,

(i) if the agreement of merger or other instrument governing the consideration to be issued provides for a cash purchase price exclusively, the cash purchase price that shall be paid in exchange for one share of Hybridon or Isis Common Stock, as the case may be, pursuant to the terms of the agreement of merger or other instrument governing the consideration to be issued;

(ii) if the agreement of merger or other instrument governing the consideration to be issued provides for a fixed exchange ratio exclusively pursuant to which each share of Hybridon or Isis Common Stock, as the case may be, will be exchanged in the Change in Control Transaction solely for capital stock of the acquiror or other surviving entity (the acquiror or other surviving entity, the "Surviving Entity"), the value of the shares of capital stock of the Surviving Entity exchanged for one share of Hybridon or Isis Common Stock, as the case may be, pursuant to the terms of the agreement of merger or other instrument governing the consideration to be issued, which value shall be determined by multiplying:

(A) the average of the midpoint of the high and low sale price of a share of such Surviving Entity's capital stock on the Stock Market on which such capital stock is traded for the 20 trading days immediately preceding the date the Change in Control Transaction is consummated (or, if the Surviving Entity is not traded on a Stock Market, the fair market value of a share of such Surviving Entity's capital stock on the date immediately preceding the date the Change in Control Transaction is consummated, as determined in good faith by the board of directors of the Party which is a party to the Change in Control Transaction), by

(B) the number of shares of such Surviving Entity's capital stock to be exchanged in the Change in Control Transaction for each share of Hybridon or Isis Common Stock, pursuant to the terms of the agreement of merger

or other instrument governing the consideration to be issued;

(iii) if the agreement of merger or other instrument governing the consideration to be issued provides that the number of shares of capital stock of the Surviving Entity to be issued in exchange for one share of Hybridon or Isis Common

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Stock, as the case may be, shall be determined based on a fixed dollar amount of the Surviving Entity's capital stock, the fixed dollar value attributed by the parties to the Change in Control Transaction to one share of Hybridon or Isis Common Stock, as the case may be, pursuant to the terms of the agreement of merger or other instrument governing the consideration to be issued; or

(iv) if the agreement of merger or other instrument governing the consideration to be issued provides that the consideration to be exchanged in the Change in Control Transaction for one share of Hybridon or Isis Common Stock, as the case may be, shall consist of any combination of cash, stock (including stock issued pursuant to a fixed exchange ratio or a fixed dollar value) or other property of the Surviving Entity, the value of the consideration to be exchanged in the Change in Control Transaction for one share of Hybridon or Isis Common Stock, as the case may be, as determined in good faith by the Board of Directors of the Party which is a party to the Change in Control Transaction, which determination shall reflect the valuation methodologies provided in clauses (i), (ii) and/or (iii) above to the extent that an element or elements of the consideration is covered by clauses (i), (ii) and/or (iii);

PROVIDED, HOWEVER, that in determining Per Share Transaction Value under this subparagraph (b) no consideration shall be given to any earn-outs or any other future payments to be determined after the consummation of the Change in Control Transaction, except any payments of amounts held in escrow; or

(c) in the case of a Type C Change in Control Transaction, the Market Price as of the date that such Change in Control Transaction becomes effective.

"RESTRICTION PERIOD" shall mean ten (10) years or such lesser period as is provided for in SECTION 8.8, in the case of Hybridon, or in SECTION 8.9, in the case of Isis.

"SECURITIES ACT" means the Securities Act of 1933, as amended.

"STOCK MARKET" means the New York Stock Exchange, the American Stock Exchange, the Nasdaq National Market, or the OTC Bulletin Board.

"TRANSACTION DOCUMENTS" means this Master Agreement, the License Agreement, and any other document or agreement executed in connection herewith or therewith on the Effective Date.

ARTICLE 2

COLLABORATION AND LICENSE AGREEMENT AND OTHER CONSIDERATION

2.1 EXECUTION OF COLLABORATION AND LICENSE AGREEMENT. Subject to and upon the terms and conditions set forth in this Master Agreement, and in reliance upon the respective

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representations and warranties made herein by each of the Parties on the Effective Date, each of Hybridon and Isis shall execute and deliver to the other the Collaboration and License Agreement attached hereto as EXHIBIT A (the "LICENSE AGREEMENT").

2.2 ADDITIONAL HYBRIDON CONSIDERATION.

(a) HYBRIDON TRANCHE PAYMENTS. In consideration for the agreements contained in this Master Agreement, and the licenses contemplated by the License Agreement, unless paid or issued earlier pursuant to SECTION 2.2(b), on the next business day following the end of each Hybridon Tranche Period,

Hybridon shall issue to Isis a number of shares of Hybridon Common Stock equal to \$2,000,000 divided by the Hybridon Market Price as of the last day of such Hybridon Tranche Period; provided however, that if such Hybridon Market Price is greater than the Hybridon Maximum Price applicable to such Hybridon Tranche Period then such Hybridon Market Price shall be deemed to be the Hybridon Maximum Price applicable to such Hybridon Tranche Period for purposes of calculating the number of shares issuable hereunder for such Hybridon Tranche Period; and provided further, that if such Hybridon Market Price is less than the Hybridon Minimum Price, then such Hybridon Market Price shall be deemed to be the Hybridon Minimum Price for purposes of calculating the number of shares issuable hereunder for such Hybridon Tranche Period.

(b) ACCELERATION OF HYBRIDON TRANCHE PAYMENTS.

(i) ACCELERATION EVENTS DURING FIRST HYBRIDON TRANCHE PERIOD. If at any time after the Effective Date the Hybridon Market Price as of any date on or before the last day of the first Hybridon Tranche Period:

(A) is greater than \$5.00, then within ten (10) business days of such date, Hybridon shall issue to Isis 1,566,667 shares of Hybridon Common Stock less any shares previously issued or then issuable to Isis pursuant to SECTIONS 2.2(b)(i)(B) or (C), in lieu of all Hybridon Tranche Payments, and upon such date Hybridon shall have no further obligations under this SECTION 2.2 other than to issue the shares of Hybridon Common Stock that are otherwise issuable as of such date and as provided for under this SECTION 2.2(b)(i)(A).

(B) is greater than \$4.00, but not greater than \$5.00, then within ten (10) business days of such date, Hybridon shall issue to Isis 1,166,667 shares of Hybridon Common Stock less any shares previously issued or then issuable to Isis pursuant to SECTION 2.2(b)(i)(C), in lieu of the first and second Hybridon Tranche Payments, and upon such date Hybridon shall have no further obligations under SECTION 2.2 with respect to the first and second Hybridon Tranche Periods, under this SECTION 2.2(b)(i)(B) or under SECTION 2.2(b)(i)(C) other than to issue the shares of Hybridon Common Stock that are otherwise issuable as of such date and as provided for under this SECTION 2.2(b)(i)(B).

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(C) is greater than \$3.00, but not greater than \$4.00, then within ten (10) business days of such date, Hybridon shall issue to Isis 666,667 shares of Hybridon Common Stock in lieu of the first Hybridon Tranche Payment and upon such date Hybridon shall have no further obligations under SECTION 2.2 with respect to the first Hybridon Tranche Period or under this SECTION 2.2(b)(i)(C) other than to issue the shares of Hybridon Common Stock provided for under this SECTION 2.2(b)(i)(C).

(ii) ACCELERATION EVENTS DURING SECOND HYBRIDON TRANCHE PERIOD. If the Hybridon Market Price as of any date which ends after the last day of the first Hybridon Tranche Period and on or before the last day of the second Hybridon Tranche Period:

(A) is greater than \$5.00, then within ten (10) business days of such date, Hybridon shall issue to Isis 900,000 shares (or 400,000 shares if shares have been previously issued or are then issuable to Isis pursuant to SECTION 2.2(b)(i)(B)) of Hybridon Common Stock less any shares previously issued or then issuable to Isis pursuant to SECTION 2.2(b)(ii)(B), in lieu of all remaining Hybridon Tranche Payments, and upon such date Hybridon shall have no further obligations under this SECTION 2.2 other than to issue the shares of Hybridon Common Stock that are otherwise issuable as of such date and as provided for under this SECTION 2.2(b)(ii)(A).

(B) is greater than \$4.00, but not greater than \$5.00, and no shares have been previously issued or are then issuable to Isis pursuant to SECTION 2.2(b)(i)(B), then within ten (10) business days of such date, Hybridon shall issue to Isis 500,000 shares of Hybridon Common Stock in lieu of the second Hybridon Tranche Payment, and upon such

date Hybridon shall have no further obligations under SECTION 2.2 with respect to the second Hybridon Tranche Period or under this SECTION 2.2(b)(ii)(B) other than to issue the shares of Hybridon Common Stock provided for under this SECTION 2.2(b)(ii)(B).

(C) is less than \$1.00, then within ten (10) business days of such date, Hybridon shall, at its option, either: (x) issue to Isis 4,000,000 shares (or 2,000,000 shares if shares have been previously issued or are then issuable to Isis pursuant to either SECTION 2.2(b)(i)(B) or SECTION 2.2(b)(ii)(B)) of Hybridon Common Stock or (y) pay to Isis \$4,000,000 (or \$2,000,000 if shares have been previously issued or are then issuable to Isis pursuant to either SECTION 2.2(b)(i)(B) or 2.2(b)(ii)(B)), in lieu of all remaining Hybridon Tranche Payments, and upon such date Hybridon shall have no further obligations under this SECTION 2.2 other than to issue the shares of Hybridon Common Stock that are otherwise issuable as of such date and to issue the shares of Hybridon Common Stock or pay the cash provided for under this SECTION 2.2(b)(ii)(C).

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(iii) ACCELERATION EVENTS DURING THIRD HYBRIDON TRANCHE PERIOD. If the Hybridon Market Price as of any date which ends after the last day of the second Hybridon Tranche Period and on or before the last day of the third Hybridon Tranche Period:

(A) is greater than \$5.00, then within ten (10) business days of such date, Hybridon shall issue to Isis 400,000 shares of Hybridon Common Stock in lieu of all remaining Hybridon Tranche Payments, and upon such date Hybridon shall have no further obligations under this SECTION 2.2 other than to issue the shares of Hybridon Common Stock that are otherwise issuable as of such date and as provided for under this SECTION 2.2(b)(iii)(A).

(B) is less than \$1.00, then within ten (10) business days of such date, Hybridon shall, at its option, either (x) issue to Isis 2,000,000 shares of Hybridon Common Stock or (y) pay to Isis \$2,000,000, in lieu of all remaining Hybridon Tranche Payments, and upon such date Hybridon shall have no further obligations under this SECTION 2.2 other than to issue the shares of Hybridon Common Stock that are otherwise issuable as of such date and to issue the shares of Hybridon Common Stock or pay the cash provided for under this SECTION 2.2(b)(iii)(B).

(iv) ACCELERATION FOR CHANGE IN CONTROL TRANSACTIONS. In the event of a Type A, Type B or Type C Change in Control Transaction that will be consummated prior to the third Hybridon Tranche Payment Date (such consummation date, the "HYBRIDON CLOSING DATE"), then immediately prior to such Hybridon Closing Date (or in the event of a Type C Change in Control Transaction, within five business days of such Hybridon Closing Date), in lieu of ALL OTHER remaining payments or share issuance obligations under this SECTION 2.2 (other than those Hybridon Tranche Payments for which the applicable Hybridon Tranche Payment Date is prior to the Hybridon Closing Date), Hybridon shall issue to Isis such number of shares of Hybridon Common Stock as is equal to the following:

\$2,000,000 DIVIDED BY the Per Share Transaction Value of such Change in Control Transaction, PROVIDED, HOWEVER, that if the Per Share Transaction Value is less than the Hybridon Minimum Price, then the \$2,000,000 shall instead be DIVIDED BY the Hybridon Minimum Price, and, PROVIDED FURTHER, that if the Per Share Transaction Value is greater than the Hybridon Maximum Price applicable to the third Hybridon Tranche Period, then the \$2,000,000 shall instead be DIVIDED BY such Hybridon Maximum Price.

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PLUS, IF AND ONLY IF the Hybridon Closing Date is prior to the second Hybridon Tranche Payment Date:

an additional \$2,000,000 DIVIDED BY the Per Share Transaction Value of such Change in Control Transaction, PROVIDED, HOWEVER, that if the Per Share Transaction Value is less than the Hybridon Minimum Price, then the \$2,000,000 shall instead be DIVIDED BY the Hybridon Minimum Price and PROVIDED FURTHER that if the Per Share Transaction Value is greater than the Hybridon Maximum Price applicable to the second Hybridon Tranche Period, then the \$2,000,000 shall instead be DIVIDED BY such Hybridon Maximum Price.

PLUS, IF AND ONLY IF the Hybridon Closing Date will be or is prior to the first Hybridon Tranche Payment Date:

an additional \$2,000,000 DIVIDED BY the Per Share Transaction Value of such Change in Control Transaction, PROVIDED, HOWEVER, that if the Per Share Transaction Value is less than the Hybridon Minimum Price, then the \$2,000,000 shall instead be DIVIDED BY the Hybridon Minimum Price and PROVIDED FURTHER that if the Per Share Transaction Value is greater than the Hybridon Maximum Price applicable to the first Hybridon Tranche Period, then the \$2,000,000 shall instead be DIVIDED BY that Hybridon Maximum Price.

(v) TYPE D CHANGE IN CONTROL TRANSACTION. On each Hybridon Tranche Payment Date from and after the occurrence of a Type D Change in Control Transaction, Hybridon shall pay to Isis \$2,000,000 in cash in lieu of the shares of Hybridon Common Stock that Hybridon would otherwise be required to issue to Isis on such Hybridon Tranche Payment Date.

(vi) Notwithstanding the other provisions of this SECTION 2.2(b), if Hybridon would be obligated under this Master Agreement to issue a number of shares of Hybridon Common Stock as would subject such issuance to the approval of Hybridon's stockholders under the rules and regulations of any Stock Market on which the Hybridon Common Stock is then traded, Hybridon may elect to not seek or obtain such approval and instead may issue such lesser number of shares as would not require such approval and may satisfy the balance of its obligation by a cash payment.

(c) SUCCESSOR ENTITIES. In the event that Hybridon consummates a merger, consolidation, reorganization, share exchange or business combination which does not qualify as a Change in Control Transaction and Hybridon is not the surviving corporation or entity following the consummation of such merger, consolidation, reorganization, share exchange or

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business combination, then Hybridon shall cause such surviving corporation or entity to comply with and be bound by and subject to (i) the provisions of SECTIONS 2.2(a) and (b), including requiring the surviving corporation or entity to issue common stock of such surviving corporation or entity to Isis, and (ii) the registration obligations and other provisions of this Master Agreement related to the stock so issued by such surviving corporation or entity, to the same extent as such provisions were applicable to Hybridon prior to the consummation of such merger, consolidation, reorganization, share exchange or business combination.

2.3 ADDITIONAL ISIS CONSIDERATION.

(a) INITIAL CASH PAYMENT AND ISIS TRANCHE PAYMENTS. In consideration for the agreements contained in this Master Agreement and the licenses contemplated by the License Agreement, Isis shall: (i) unconditionally, and irrespective of any breach of this Master Agreement or the License Agreement by Hybridon, on or prior to 5:00 p.m. (Boston time), on Friday, June 1, 2001, pay to Hybridon by wire transfer in immediately available funds, the sum of Fifteen Million Dollars (\$15,000,000), and (ii) unless paid or issued earlier pursuant to SECTION 2.3(b), on the next business day following the end of each Isis Tranche Period, issue to Hybridon such number of shares of Isis Common

Stock equal to \$5,000,000 (\$4,500,000 in the case of the fourth Isis Tranche Period), divided by the Isis Market Price as of the last day of such Isis Tranche Period; provided, however, that if such Isis Market Price is greater than the Isis Maximum Price applicable to such Isis Tranche Period, then such Isis Market Price shall be deemed to be the Isis Maximum Price applicable to such Isis Tranche Period for purposes of calculating the number of shares issuable hereunder for such Isis Tranche Period; and provided, further, that if such Isis Market Price is less than the Isis Minimum Price applicable to such Isis Tranche Period, then such Isis Market Price shall be deemed to be the Isis Minimum Price applicable to such Isis Tranche Period for purposes of calculating the number of shares issuable hereunder for such Isis Tranche Period. The Parties acknowledge and agree that all payments to be made to Hybridon by Isis pursuant to this Master Agreement will allow Hybridon to recoup the expenditures incurred by Hybridon in the research and development of antisense technology undertaken by Hybridon.

(b) ACCELERATION OF ISIS TRANCHE PAYMENTS

(i) ACCELERATION EVENTS DURING FIRST ISIS TRANCHE PERIOD. If at any time after the Effective Date the Isis Market Price as of any date which ends on or before the last day of the first Isis Tranche Period:

(A) is greater than \$26.00, then within ten (10) business days of such date, Isis shall issue to Hybridon 1,030,220 shares of Isis Common Stock less any shares previously issued or then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(B) or SECTION 2.3(b)(i)(C), in lieu of all Isis Tranche Payments, and upon such date Isis shall have no further obligations under this SECTION 2.3 other than to

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issue the shares of Isis Common Stock that are otherwise issuable on such date and as provided for under this SECTION 2.3(b)(i)(A).

(B) is greater than \$20.00, but not greater than \$26.00, then within ten (10) business days of such date, Isis shall issue to Hybridon 857,143 shares of Isis Common Stock less any shares previously issued or then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(C), in lieu of the first, second and third Isis Tranche Payments, and upon such date Isis shall have no further obligations under SECTION 2.3 with respect to the first, second and third Isis Tranche Periods, under this SECTION 2.3(b)(i)(B) or under SECTION 2.3(b)(i)(C) other than to issue the shares of Isis Common Stock that are otherwise issuable on such date and as provided for under this SECTION 2.3(b)(i)(B).

(C) is greater than \$14.00, but not greater than \$20.00, then within ten (10) business days of such date, Isis shall issue to Hybridon 357,143 shares of Isis Common Stock in lieu of the first Isis Tranche Payment, and upon such date Isis shall have no further obligations under SECTION 2.3 with respect to the first Isis Tranche Period or under this SECTION 2.3(b)(i)(C) other than to issue the shares of Isis Common Stock provided for under this SECTION 2.3(b)(i)(C).

(D) is less than \$3.00, then within ten (10) business days of such date, Isis shall, at its option either: (x) issue to Hybridon 2,785,714 shares less any shares previously issued or are then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(B) or SECTION 2.3(b)(i)(C), or (y) pay to Hybridon \$19,500,000 (or \$4,500,000 if shares have been previously issued or are then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(B) or \$14,500,000 if shares have been previously issued or are then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(C)), in lieu of all remaining Isis Tranche Payments, and upon such date Isis shall have no further obligations under this SECTION 2.3 other than to issue the shares of Isis Common Stock that are otherwise issuable on such date and to issue the shares of Isis Common Stock or pay the cash provided for under this SECTION 2.3(b)(i)(D).

(ii) ACCELERATION EVENTS DURING SECOND ISIS TRANCHE PERIOD. If the Isis Market Price as of any date which ends after the last day of the first Isis Tranche Period and on or before

the last day of the second Isis Tranche Period:

(A) is greater than \$26.00, then within ten (10) business days of such date, Isis shall issue to Hybridon 673,077 shares (or 173,077 shares in the event shares have been previously issued or are then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(B) or SECTION 2.3(b)(ii)(B)) of Isis Common Stock in lieu of all remaining Isis Tranche Payments, and upon such date Isis shall have no further obligations under this SECTION 2.3 other than to issue the shares of Isis

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Common Stock that are otherwise issuable on such date and as provided for under this SECTION 2.3(b)(ii)(A).

(B) is greater than \$20.00, but less than \$26.00, and no shares have been previously issued or are then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(B), then within ten (10) business days of such date, Isis shall issue to Hybridon 500,000 shares of Isis Common Stock in lieu of the second and third Isis Tranche Payments, and upon such date Isis shall have no further obligations under SECTION 2.3 with respect to the second and third Isis Tranche Periods or under this SECTION 2.3(b)(ii)(B) other than to issue shares of Isis Common Stock provided for under this SECTION 2.3(b)(ii)(B).

(C) is less than \$3.00, then within ten (10) business days of such date, Isis shall, at its option, either: (x) issue to Hybridon 2,071,429 shares (or 642,857 shares if shares have been previously issued or are then issuable to Hybridon pursuant to either SECTION 2.3(b)(i)(B) or SECTION 2.3(b)(ii)(B)) of Isis Common Stock or (y) pay to Hybridon \$14,500,000 (or \$4,500,000 if shares have been previously issued or are then issuable to Hybridon pursuant to either SECTION 2.3(b)(i)(B) or SECTION 2.3(b)(ii)(B)), in lieu of all remaining Isis Tranche Payments, and upon such date Isis shall have no further obligations under this SECTION 2.3 other than to issue the shares of Isis Common Stock that are otherwise issuable on such date and to issue the shares of Isis Common Stock or pay the cash provided for under this SECTION 2.3(b)(ii)(C).

(iii) ACCELERATION EVENTS DURING THIRD ISIS TRANCHE PERIOD. If the Isis Market Price as of any date which ends after the last day of the second Isis Tranche Period and on or before the last day of the third Isis Tranche Period:

(A) is greater than \$26.00, then within ten (10) business days of such date, Isis shall issue to Hybridon 423,077 shares (or 173,077 shares if shares have been previously issued or are then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(B), SECTION 2.3(b)(ii)(B) or SECTION 2.3(b)(iii)(B)) of Isis Common Stock, in lieu of all remaining Isis Tranche Payments, and upon such date Isis shall have no further obligations under this SECTION 2.3 other than to issue the shares of Isis Common Stock that are otherwise issuable on such date and as provided for under this SECTION 2.3(b)(iii)(A).

(B) is greater than \$20.00, but not greater than \$26.00, and no shares have been previously issued or are then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(B) or SECTION 2.3(b)(ii)(B), then within ten (10) business days of such date, Isis shall issue to Hybridon 250,000 shares of Isis Common Stock in lieu of the third Isis Tranche Payments, and upon such date Isis shall have no further obligations under SECTION 2.3 with respect to the third Isis Tranche Period

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or under this SECTION 2.3(b)(iii)(B) other than to issue the shares of Isis Common Stock provided for under this

SECTION 2.3(b)(iii)(B).

(C) is less than \$7.00, then within ten (10) business days of such date, Isis shall, at its option, either: (x) issue to Hybridon 1,357,143 shares (or 642,857 shares if shares have been previously issued or are then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(B), SECTION 2.3(b)(ii)(B) or SECTION 2.3(b)(iii)(B)) of Isis Common Stock or (y) pay to Hybridon \$9,500,000 (or \$4,500,000 if shares have been previously issued or are then issuable to Hybridon pursuant to SECTION 2.3(b)(i)(B), SECTION 2.3(b)(ii)(B) or SECTION 2.3(b)(iii)(B)), in lieu of all remaining Isis Tranche Payments, and upon such date Isis shall have no further obligations under this SECTION 2.3 other than to issue the shares of Isis Common Stock that are otherwise issuable on such date and to issue the shares of Isis Common Stock or pay the cash provided for under this SECTION 2.3(b)(iii)(C).

(iv) ACCELERATION EVENTS DURING FOURTH ISIS TRANCHE PERIOD. If the Isis Market Price as of any date which ends after the last day of the third Isis Tranche Period and on or before the last day of the fourth Isis Tranche Period:

(A) is greater than \$26.00, then within ten (10) business days of such date, Isis shall issue to Hybridon 173,077 shares of Isis Common Stock in lieu of all remaining Isis Tranche Payments, and upon such date Isis shall have no further obligations under this SECTION 2.3 other than to issue the share of Isis Common Stock that are otherwise issuable on such date and as provided for under this SECTION 2.3(b)(iv)(A).

(B) is less than \$7.00, then within ten (10) business days of such date, Isis shall, at its option either: (x) issue to Hybridon 642,857 shares of Isis Common Stock or (y) pay Hybridon \$4,500,000, in lieu of all remaining Isis Tranche Payments, and upon such date Isis shall have no further obligations under this SECTION 2.3 other than to issue the shares of Isis Common Stock that are otherwise issuable on such date and to issue the shares of Isis Common Stock or pay the cash provided for under this SECTION 2.3(b)(iv)(B).

(v) ACCELERATION FOR CHANGE IN CONTROL TRANSACTIONS. In the event of a Type A, Type B or Type C Change in Control Transaction that will be consummated prior to the fourth Isis Tranche Payment Date (such consummation date, the "ISIS CLOSING DATE"), then immediately prior to such Isis Closing Date (or in the event of a Type C Change in Control Transaction, within five business days of such Isis Closing Date), in lieu of ALL OTHER remaining payments or share issuance obligations under this SECTION 2.3 (other than those Isis Tranche Payments for which the applicable Isis Tranche Payment Date is prior to the Isis Closing Date), Isis shall issue to Hybridon such number of shares of Isis Common Stock as is equal to the following:

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\$4,500,000 DIVIDED BY the Per Share Transaction Value, PROVIDED, HOWEVER, that if the Per Share Transaction Value is less than the Isis Minimum Price applicable to the fourth Isis Tranche Period, then the \$4,500,000 shall instead be DIVIDED BY the Isis Minimum Price applicable to the fourth Isis Tranche Period, and, PROVIDED FURTHER, that if the Per Share Transaction Value is greater than the Isis Maximum Price applicable to the fourth such Isis Tranche Period, then the \$4,500,000 shall instead be DIVIDED BY such Isis Maximum Price.

PLUS, IF AND ONLY IF the Isis Closing Date will be or is prior to the third Isis Tranche Payment Date:

an additional \$5,000,000 DIVIDED BY the Per Share Transaction Value, PROVIDED, HOWEVER, that if Per Share Transaction Price is less than the Isis Minimum Price applicable to the third Isis Tranche Period, then the

\$5,000,000 shall instead be DIVIDED BY the Isis Minimum Price applicable to the third Isis Tranche Period, and, PROVIDED FURTHER, that if the Per Share Transaction Value is greater than the Isis Maximum Price applicable to the third Isis Tranche Period, then the \$5,000,000 shall instead be DIVIDED BY such Isis Maximum Price.

PLUS, IF AND ONLY IF the Isis Closing Date will be or is prior to the second Isis Tranche Payment Date:

an additional \$5,000,000 DIVIDED BY the Per Share Transaction Price, PROVIDED, HOWEVER, that if the Per Share Transaction Price is less than the Isis Minimum Price applicable to the second Isis Tranche Period, then the \$5,000,000 shall instead be DIVIDED BY the Isis Minimum Price applicable to the second Isis Tranche Period, and, PROVIDED FURTHER, that if the Per Share Transaction Value is greater than the Isis Maximum Price applicable to the second Isis Tranche Period, then the \$5,000,000 shall instead be DIVIDED BY such Isis Maximum Price.

PLUS, IF AND ONLY IF the Isis Closing Date will be or is prior to the first Isis Tranche Payment Date:

an additional \$5,000,000 DIVIDED BY the Per Share Transaction Price, PROVIDED, HOWEVER, that if Per Share Transaction Price is less than the Isis Minimum Price applicable to the first Isis Tranche Period, then the \$5,000,000 shall instead be DIVIDED BY the Isis Minimum Price applicable to the first Isis Tranche Period, and,

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FURTHER PROVIDED, that if the Per Share Transaction Value is greater than the Isis Maximum Price applicable to the first Isis Tranche Period, then the \$5,000,000 shall instead be DIVIDED BY such Isis Maximum Price.

(vi) TYPE D CHANGE IN CONTROL TRANSACTION. On each Isis Tranche Payment Date from and after the occurrence of a Type D Change in Control Transaction, Isis shall pay to Hybridon \$5,000,000 (\$4,500,000 in the case of the fourth Isis Tranche Payment Date) in lieu of the shares of Isis Common Stock that Isis would otherwise be required to issue to Hybridon on such Isis Tranche Payment Date.

(vii) Notwithstanding the other provisions of this SECTION 2.3(b), if Isis would be obligated under this Master Agreement to issue a number of shares of Isis Common Stock as would subject such issuance to the approval of Isis's stockholders under the rules and regulations of the Stock Market on which the Isis Common Stock is then traded, Isis may elect to not seek or obtain such approval and instead may issue such lesser number of shares as would not require such approval and may satisfy the balance of its obligation by a cash payment.

(c) SUCCESSOR ENTITIES. In the event that Isis consummates a merger, consolidation, reorganization, share exchange or business combination which does not qualify as a Change in Control Transaction and Isis is not the surviving corporation or entity following such merger, consolidation, reorganization, share exchange or business combination, then Isis shall cause such surviving corporation or entity to comply with and be bound by and subject to (i) the provisions of SECTIONS 2.3(a) and (b), including requiring the surviving corporation or entity to issue common stock of such surviving corporation or entity to Hybridon, and (ii) the registration obligations and other provisions of this Master Agreement related to the stock so issued by Isis or such surviving corporation or entity, all to the same extent as such provisions were applicable to Isis prior to the merger, consolidation, reorganization, share exchange or business combination.

2.4 RESTRICTIVE LEGEND. Each certificate for the shares of

Hybridon Common Stock or Isis Common Stock, whichever is applicable, issuable under this ARTICLE 2 shall be stamped or otherwise imprinted with legends in substantially the following form:

"THE SECURITIES REPRESENTED BY THIS CERTIFICATE HAVE BEEN ACQUIRED FOR INVESTMENT AND HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933. NEITHER THESE SECURITIES NOR ANY INTEREST THEREIN MAY BE SOLD, PLEDGED, HYPOTHECATED, TRANSFERRED OR OTHERWISE DISPOSED OF IN THE ABSENCE OF SUCH REGISTRATION AND IN COMPLIANCE WITH APPLICABLE STATE SECURITIES LAWS OR THE DELIVERY OF AN OPINION REASONABLY SATISFACTORY TO THE COMPANY STATING THAT THERE IS A VALID EXEMPTION THEREFROM

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UNDER SUCH ACT AND THE RULES AND REGULATIONS THEREUNDER AND SUCH STATE SECURITIES LAWS."

ARTICLE 3

REPRESENTATIONS AND WARRANTIES OF HYBRIDON

As an inducement to Isis to enter into and perform its obligations under this Master Agreement and License Agreement, Hybridon hereby represents and warrants to Isis as of the date hereof as follows:

3.1 ORGANIZATION AND GOOD STANDING; POWER. Hybridon is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware and has full power and authority to execute and deliver this Master Agreement and the other Transaction Documents to which it is a party, to perform its obligations hereunder and thereunder and to consummate the transactions contemplated hereby and thereby.

3.2 AUTHORIZATION. The execution and delivery by Hybridon of this Master Agreement and the other Transaction Documents to which it is a party, the performance by Hybridon of its obligations hereunder and thereunder, and the consummation by Hybridon of the transactions contemplated hereby and thereby have been duly authorized by all necessary corporate action on the part of Hybridon. This Master Agreement and the other Transaction Documents have been duly executed and delivered by Hybridon and constitute the legal, valid and binding obligations of Hybridon, enforceable against Hybridon in accordance with their respective terms, except (a) that enforcement may be limited by (i) applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or other similar laws affecting creditors' rights, and (ii) general equity principles and limitations on the availability of equitable relief, including specific performance, and (b) that any rights to indemnity or contribution hereunder or thereunder may be limited by state and federal securities laws and by public policy considerations.

3.3 NO VIOLATION. The execution, delivery and performance by Hybridon of this Master Agreement and the other Transaction Documents to which it is a party and the consummation by Hybridon of the transactions contemplated hereby and thereby do not and will not:

(a) conflict with, result in the breach, modification, termination or violation of, or loss of any benefit under, constitute a default under, accelerate the performance required by, result in or give rise to a right to amend or modify the terms of, result in the creation of any lien upon any assets or properties, or in any manner release any party thereto from any obligation under, any mortgage, note, bond, indenture, contract, agreement, lease, license or other instrument or obligation to which Hybridon is a party or by which Hybridon's assets or property are bound;

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(b) conflict with, violate or result in any loss of benefit under, any permit, concession, franchise, order, judgment, writ, injunction, regulation, statute or decree; to which it is subject, or

(c) conflict with or violate any provision of the Certificate of Incorporation or Bylaws, each as heretofore amended, of Hybridon,

except where, in the case of (a) and (b) above, such event would not, individually or in the aggregate with other such events, adversely affect the rights of Isis under this Master Agreement and the Transaction Documents or subject Isis to any material liability (contingent or otherwise).

3.4 NO CONSENT REQUIRED. No consent, approval, order or authorization of, or declaration, filing or registration with, any person, entity or governmental authority is required to be made or obtained by Hybridon in connection with the authorization, execution, delivery or performance of this Master Agreement, the other Transaction Documents to which it is a party or the transactions contemplated hereby or thereby, except for the filing of registration statements and other reports with the Commission, filings related to compliance with the Securities Act, the Exchange Act and state securities laws and any filings with the Stock Market on which the Hybridon Common Stock is traded.

3.5 ISSUANCE. The shares of Hybridon Restricted Stock to be delivered by Hybridon hereunder have been duly authorized and, when issued and delivered in accordance with the terms of this Master Agreement, will be validly issued, fully paid and non-assessable and will not be issued in violation of any preemptive rights, rights of first refusal or similar rights.

3.6 LITIGATION. There is no litigation or governmental or administrative proceeding or investigation pending or, to the knowledge of Hybridon, threatened in writing against Hybridon or its Affiliates which, individually or in the aggregate, reasonably would be expected to have a material adverse effect on the Hybridon Intellectual Property or which would prevent or hinder Hybridon from performing its obligations under this Master Agreement or the other Transaction Documents to which it is a party.

3.7 INVESTMENT REPRESENTATIONS.

(a) Hybridon is capable of evaluating the merits and risks of an investment in Isis Restricted Stock. Hybridon has not been formed solely for the purpose of entering into the transactions contemplated in this Master Agreement and is acquiring the Isis Restricted Stock for investment for its own account, not as a nominee or agent, and not with the view to, or for resale, distribution or fractionalization thereof (except in connection with a registered offering), in whole or in part, and no other person has a direct or indirect interest, beneficial or otherwise in the Isis Restricted Stock, except in compliance with securities laws.

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(b) Hybridon acknowledges its understanding that the private placement and sale to Hybridon of the Isis Restricted Stock to it is exempt from registration under the Securities Act by virtue of the provisions of Regulation D. In furtherance thereof, Hybridon represents and warrants that it is an "accredited investor" as that term is defined in Regulation D.

(c) Hybridon agrees that it shall not sell or otherwise transfer any of the Isis Restricted Stock without registration under the Securities Act unless it shall deliver to Isis an opinion of counsel reasonably satisfactory to Isis that an exemption from registration is available. Hybridon fully understands and agrees that it must bear the total economic risk of its purchase of Isis Restricted Stock for an indefinite period of time because, among other reasons, the Isis Restricted Stock will not have been registered under the Securities Act or under the securities laws of any applicable state or other jurisdiction and, therefore, cannot be resold, pledged, assigned or otherwise disposed of unless subsequently registered under the Securities Act and under applicable state securities laws or unless an exemption from such registration is available. Hybridon understands that Isis is under no obligation to register the Isis Restricted Stock on its behalf with the exception of certain registration rights as set forth herein. Hybridon understands the lack of liquidity and the restrictions on transfer on the Isis Restricted Stock and that the acquisition of Isis Restricted Stock is suitable only for a person or entity of adequate financial means that has no need for liquidity of its investment and that can afford a total loss of its investment.

3.8 SEC FILINGS. Except for the filing of its Annual Report on Form 10-K for the year ended December 31, 1999, which was not timely filed, since January 1, 1998, Hybridon has filed with the Commission all forms, reports, schedules, statements, exhibits and other documents (collectively, the "SEC FILINGS") required to be filed by Hybridon pursuant to Section 13, 14 or 15(d) of the Exchange Act on or before the date required to be filed with the Commission. At the time filed, Hybridon's SEC Filings, including without limitation, any financial statements, exhibits and schedules included therein or documents incorporated therein by reference, to Hybridon's knowledge, (i) did not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading and (ii) complied in all material respects with the applicable requirements of the Securities Act or the Exchange Act, as the case may be.

3.9 BROKERS OR FINDERS. There have been no investment bankers, brokers or finders used by Hybridon in connection with the transactions contemplated by the Transactions Documents and no such persons or entities are entitled to a fee or compensation in respect thereof.

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ARTICLE 4

REPRESENTATIONS AND WARRANTIES OF ISIS

As an inducement to Hybridon to enter into and perform its obligations under this Master Agreement and the License Agreement, Isis hereby represents and warrants to Hybridon as of the date hereof as follows:

4.1 ORGANIZATION AND GOOD STANDING; POWER. Isis is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware and has full power and authority to execute and deliver this Master Agreement and the other Transaction Documents to which it is a party, to perform its obligations hereunder and thereunder and to consummate the transactions contemplated hereby and thereby.

4.2 AUTHORIZATION. The execution and delivery by Isis of this Master Agreement and the other Transaction Documents to which it is a party, the performance by Isis of its obligations hereunder and thereunder, and the consummation by Isis of the transactions contemplated hereby and thereby have been duly authorized by all necessary corporate action on the part of Isis. This Master Agreement and the other Transaction Documents have been duly executed and delivered by Isis and constitute the legal, valid and binding obligations of Isis, enforceable against Isis in accordance with their respective terms, except (a) that enforcement may be limited by (i) applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or other similar laws affecting creditors' rights, and (ii) general equity principles and limitations on the availability of equitable relief, including specific performance, and (b) that any rights to indemnity or contribution hereunder or thereunder may be limited by state and federal securities laws and by public policy considerations.

4.3 NO VIOLATION. The execution, delivery and performance by Isis of this Master Agreement and the other Transaction Documents to which it is a party and the consummation by Isis of the transactions contemplated hereby and thereby do not and will not:

(a) conflict with, result in the breach, modification, termination or violation of, or loss of any benefit under, constitute a default under, accelerate the performance required by, result in or give rise to a right to amend or modify the terms of, result in the creation of any lien upon any assets or properties, or in any manner release any party thereto from any obligation under, any material mortgage, note, bond, indenture, contract, agreement, lease, license or other instrument or obligation to which Isis is a party or Isis's assets or property are bound;

(b) conflict with, violate or result in any loss of benefit under, any permit, concession, franchise, order, judgment, writ, injunction, regulation, statute or decree to which it is subject; or

(c) conflict with or violate any provision of the Certificate of Incorporation or Bylaws, each as heretofore amended, of Isis,

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except where, in the case of (a) and (b) above, such event would not, individually or in the aggregate with other such events, adversely affect the rights of Hybridon under this Master Agreement and the other Transaction Documents or subject Hybridon to any material liability (contingent or otherwise).

4.4 NO CONSENT REQUIRED. No consent, approval, order or authorization of, or declaration, filing or registration with, any person, entity or governmental authority is required to be made or obtained by Isis in connection with the authorization, execution, delivery or performance of this Master Agreement, the other Transaction Documents to which it is a party or the transactions contemplated hereby or thereby, except for the filing of registration statements and other reports with the Commission, filings related to compliance with the Securities Act, the Exchange Act and state securities laws and any filings with the Stock Market on which the Isis Common Stock is listed.

4.5 ISSUANCE. The shares of Isis Restricted Stock to be delivered by Isis hereunder have been duly authorized and, when issued and delivered in accordance with the terms of this Master Agreement, will be validly issued, fully paid and non-assessable and will not be issued in violation of any preemptive rights, rights of first refusal or similar rights.

4.6 LITIGATION. There is no litigation or governmental or administrative proceeding or investigation pending or, to the knowledge of the Isis, threatened in writing against Isis or its Affiliates which, individually or in the aggregate, reasonably would be expected to have a material adverse effect on the Isis Intellectual Property or which would prevent or hinder Isis from performing its obligations under this Master Agreement or the other Transaction Documents to which it is a party.

4.7 INVESTMENT REPRESENTATIONS.

(a) Isis is capable of evaluating the merits and risks of an investment in Hybridon Restricted Stock. Isis has not been formed solely for the purpose of entering into the transactions contemplated in this Master Agreement and is acquiring the Hybridon Restricted Stock for investment for its own account, not as a nominee or agent, and not with the view to, or for resale, distribution or fractionalization thereof, (except in connection with a registered offering), in whole or in part, and no other person has a direct or indirect interest, beneficial or otherwise in the Hybridon Restricted Stock.

(b) Isis acknowledges its understanding that the private placement and sale to Isis of the Hybridon Restricted Stock to it is exempt from registration under the Securities Act by virtue of the provisions of Regulation D. In furtherance thereof, Isis represents and warrants that it is an "accredited investor" as that term is defined in Regulation D.

(c) Isis agrees that it shall not sell or otherwise transfer any of the Hybridon Restricted Stock without registration under the Securities Act unless it shall deliver to Hybridon an opinion of counsel reasonably satisfactory to Isis that an exemption from registration is

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available. Isis fully understands and agrees that it must bear the total economic risk of its purchase of Hybridon Restricted Stock for an indefinite period of time because, among other reasons, the Hybridon Restricted Stock will not have been registered under the Securities Act or under the securities laws of any applicable state or other jurisdiction and, therefore, cannot be resold, pledged, assigned or otherwise disposed of unless subsequently registered under the Securities Act and under applicable state securities laws or unless an exemption from such registration is available. Isis understands that Hybridon is under no obligation to register the Hybridon Restricted Stock on its behalf with the exception of certain registration rights as set forth herein. Isis understands the lack of liquidity and the restrictions on transfer on the Hybridon Restricted Stock and that the acquisition of Hybridon Restricted Stock is suitable only for a person or entity of adequate financial means that has no need for liquidity of its investment and that can afford a total loss of its investment.

4.8 SEC FILINGS. Since January 1, 1998, Isis has filed with the Commission all SEC Filings required to be filed by Isis pursuant to Section 13, 14 or 15(d) of the Exchange Act on or before the date required to be filed with the Commission. At the time filed, Isis's SEC Filings, including without limitation, any financial statements, exhibits and schedules included therein or documents incorporated therein by reference, to Isis's knowledge, (i) did not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading and (ii) complied in all material respects with the applicable requirements of the Securities Act or the Exchange Act, as the case may be.

4.9 BROKERS OR FINDERS. There have been no investment bankers, brokers or finders used by Isis in connection with the transactions contemplated by the Transactions Documents and no such persons or entities are entitled to a fee or compensation in respect thereof.

ARTICLE 5

CLOSING DELIVERIES OF ISIS

Isis hereby unconditionally agrees, irrespective of any breach of this Master Agreement or the License Agreement by Hybridon, to deliver to Hybridon at or prior to 5:00 p.m. (Boston time) on Friday, June 1, 2001:

(a) An executed counterpart of the License Agreement;

(b) A certificate of the appropriate officer of Isis certifying as to the resolutions adopted by the board of directors authorizing the execution, delivery, and performance by Isis of this Master Agreement and the License Agreement and the consummation of the transactions contemplated hereby and thereby;

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(c) An opinion of counsel to Isis which shall address the Isis Common Stock to be issued under this Master Agreement in regards to its due authorization and, when issued, its being legally and validly issued, fully paid and non-assessable.

(d) The cash payment referred to in SECTION 2.3(a) above.

ARTICLE 6

CLOSING DELIVERIES OF HYBRIDON

Isis shall have received at or prior to the Effective Date:

(a) An executed counterpart of the License Agreement;

(b) A certificate of the appropriate officer of Hybridon certifying as to the resolutions adopted by the board of directors authorizing the execution, delivery, and performance by Hybridon of this Master Agreement and the License Agreement and the consummation of the transactions contemplated hereby and thereby; and

(c) An opinion of counsel to Hybridon which shall address the Hybridon Common Stock to be issued under this Master Agreement in regards to its due authorization, and, when issued, its being legally and validly issued, fully paid and non-assessable.

ARTICLE 7

REGISTRATION RIGHTS

7.1 HYBRIDON REGISTRATION OBLIGATIONS.

(a) For each issuance of Hybridon Common Stock hereunder, Hybridon shall, at its own expense:

(i) prepare and file, within ten (10) business days of each such issuance of Hybridon Common Stock, with the Commission a registration statement to register for resale on the Stock Market on which Hybridon's Common Stock is then traded, the Hybridon Common Stock so issued and use its best efforts to cause such registration statement to be declared effective by the Commission as promptly as practicable; and

(ii) prepare and file with the Commission such amendments and supplements to such registration statement and the prospectus used in connection therewith as may be necessary to keep such registration statement effective until the first anniversary of the date of such issuance of Hybridon Common Stock, or, if earlier, until such time as Isis shall have completed the distribution of all Hybridon Common Stock

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covered by the registration statement, and comply with the provisions of the Securities Act with respect to the disposition of all securities covered by such registration statement during such effective period in accordance with the intended methods of disposition by Isis, and cause the prospectus to be supplemented by any required prospectus supplement, and as so supplemented to be filed pursuant to Rule 424 under the Securities Act. Hybridon is entitled to withdraw such registration statement at such time as it no longer is required to keep such registration statement effective under this clause (ii) and following such withdrawal Isis shall have no further right to offer or sell any Hybridon Common Stock pursuant to such registration statement; and

(iii) provide a transfer agent and registrar for

all Hybridon Common Stock so issued to Isis not later than the effective date of such registration statement.

(b) Isis will furnish to Hybridon in writing such information as Hybridon may reasonably require from Isis, and otherwise reasonably cooperate with Hybridon, in connection with any registration statement to be filed pursuant to subparagraph (a) above.

(c) Subject to SECTION 9.1, Hybridon will indemnify Isis against any and all claims, losses, damages and liabilities (or actions in respect thereof) arising out of or based on any untrue statement (or alleged untrue statement) of any material fact contained in any prospectus, offering circular or other document incident to any registration, qualification or compliance (or in any related registration statement, notification or the like) or any omission (or alleged omission) to state therein any material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances in which they were made, not misleading, or any violation by Hybridon of any rule or regulation promulgated under federal and state securities laws applicable to Hybridon and relating to any action or inaction required of Hybridon in connection with any such registration, qualification or compliance, and Hybridon will reimburse Isis for any legal and any other expenses reasonably incurred in connection with investigating or defending any such claim, loss, damage, liability or action; provided, however, that Hybridon will not be liable in any such case to the extent that any such claim, loss, damage or liability arises out of or is based on any untrue statement or omission based upon written information furnished to Hybridon in an instrument duly executed by Isis for use in such prospectus, offering circular or other document (or in any related registration statement, notification or the like).

(d) Subject to SECTION 9.1, Isis will indemnify Hybridon against any and all claims, losses, damages and liabilities (or actions in respect thereof) arising out of or based on any untrue statement (or alleged untrue statement) of any material fact contained in any prospectus, offering circular or other document incident to any registration, qualification or compliance (or in any related registration statement, notification or the like) or any omission (or alleged omission) to state therein any material fact required to be stated therein or necessary to make the statement therein, in light of the circumstance in which they were made, not misleading, and Isis will reimburse Hybridon for any legal and any other expenses reasonably

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incurred in connection with investigating or defending any such claim, loss, damage, liability or action; provided, however, that this paragraph (e) shall apply only if (and only to the extent that) such statement or omission was made in reliance upon written information furnished to Hybridon in an instrument duly executed by Isis for use in such prospectus, offering circular or other document (or related registration statement, notification or the like) or any amendment or supplement thereto; and, provided further, that Isis's liability hereunder with respect to any particular registration shall be limited to an amount equal to the net proceeds received by Isis from the Hybridon Common Stock sold by Isis under such registration statement.

7.2 ISIS REGISTRATION OBLIGATIONS.

(a) For each issuance of Isis Common Stock hereunder, Isis shall, at its own expense:

(i) prepare and file, within ten (10) business days of each such issuance of Isis Common Stock, with the Commission a registration statement to register for resale on the Stock Market on which Isis's Common Stock is then traded, the Isis Common Stock so issued and use its best efforts to cause such registration statement to be declared effective by the Commission as promptly as practicable;

(ii) prepare and file with the Commission such amendments and supplements to such registration statement and the prospectus used in connection therewith as may be necessary to keep such registration statement effective until the first anniversary of the date of such issuance of Isis Common Stock, or, if earlier, until such time as Hybridon shall have completed the distribution of all Isis Common Stock covered by the registration statement, and comply with the provisions of the Securities Act with respect to the disposition of all securities of all Isis Common Stock covered by such registration statement during such effective period in accordance with the intended methods of disposition by Hybridon, and cause the prospectus to be supplemented by any required prospectus supplement, and as so supplemented to be filed pursuant to Rule 424 under the Securities Act.

Isis is entitled to withdraw such registration statement at such time as it no longer is required to keep such registration statement effective under this clause (ii) and following such withdrawal Hybridon shall have no further right to offer or sell any Isis Common Stock pursuant to such registration statement; and

(iii) provide a transfer agent and registrar for all Isis Common Stock so issued to Hybridon not later than the effective date of such registration statement.

(b) Hybridon will furnish to Isis in writing such information as Isis may reasonably require from Hybridon, and otherwise reasonably cooperate with Isis in connection with any registration to be filed pursuant to subparagraph (a) above.

(c) Subject to SECTION 9.1, Isis will indemnify Hybridon against any and all claims, losses, damages and liabilities (or actions in respect thereof) arising out of or based on

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any untrue statement (or alleged untrue statement) of any material fact contained in any prospectus, offering circular or other document incident to any registration, qualification or compliance (or in any related registration statement, notification or the like) or any omission (or alleged omission) to state therein any material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances in which they were made, not misleading, or any violation by Isis of any rule or regulation promulgated under federal and state securities laws applicable to Isis and relating to any action or inaction required of Isis in connection with any such registration, qualification or compliance, and Isis will reimburse Hybridon for any legal and any other expenses reasonably incurred in connection with investigating or defending any such claim, loss, damage, liability or action; provided, however, that Isis will not be liable in any such case to the extent that any such claim, loss, damage or liability arises out of or is based on any untrue statement or omission based upon written information furnished to Isis in an instrument duly executed by Hybridon for use in such prospectus, offering circular or other document (or in any related registration statement notification or the like).

(d) Subject to SECTION 9.1, Hybridon will indemnify Isis against any and all claims, losses, damages and liabilities (or actions in respect thereof) arising out of or based on any untrue statement (or alleged untrue statement) of any material fact contained in any prospectus, offering circular or other document incident to any registration, qualification or compliance (or in any related registration statement, notification or the like) or any omission (or alleged omission) to state therein any material fact required to be stated therein or necessary to make the statement therein, in light of the circumstances in which they were made, not misleading, and Hybridon will reimburse Isis for any legal and any other expenses reasonably incurred in connection with investigating or defending any such claim, loss, damage, liability or action; provided, however, that this paragraph (e) shall apply only if (and only to the extent that) such statement or omission was made in reliance upon written information furnished to Isis in an instrument duly executed by Hybridon for use in such prospectus, offering circular or other document (or related registration statement, notification or the like) or any amendment or supplement thereto; and, provided further, that Hybridon's liability hereunder with respect to any particular registration shall be limited to an amount equal to the net proceeds received by Hybridon from the Isis Common Stock sold by Hybridon in such registration.

7.3 FILING REQUIREMENTS. With a view to making available to each of the Parties the benefits of Rule 144 promulgated under the Securities Act ("RULE 144") and any other rule or regulation of the SEC that may at any time permit such Parties to sell their respective shares of Hybridon Common Stock or Isis Common Stock issued under this Master Agreement to the public without registration or pursuant to a registration on Form S-3, each of Hybridon and Isis covenants and agrees to take commercially reasonable efforts to: (i) make and keep public information available, as those terms are understood and defined in Rule 144; (ii) file with the Commission in a timely manner all reports and other documents required of such Party under the Securities Act and the Exchange Act, and (iii) furnish to the other Party upon the other Party's request, (A) a copy of such Party's most recent annual or quarterly report, and (B) such other

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information as may be reasonably requested by the other Party in order to avail

the other Party of any rule or regulation of the Commission that permits the selling pursuant to a registration statement. Notwithstanding the foregoing, a Party's covenants and agreements under this SECTION 7.3 shall terminate and be of no further force or effect from and after such time as the other Party may resell all of the Common Stock of such Party issued to the other Party under this Master Agreement pursuant to paragraph (k) of Rule 144 under the Securities Act or, if earlier, such date as the other Party shall have sold or otherwise distributed all of such Common Stock.

7.4 LIMITATION ON REGISTRATION OBLIGATIONS. Notwithstanding anything in this Master Agreement to the contrary, if either Party (the "Blocking Party") shall furnish to the other Party (the "Selling Party") a certificate signed by the President or Chief Executive Officer of the Blocking Party, stating that its Board of Directors has made the good faith determination (i) that continued use by the Selling Party, of a registration statement filed pursuant to ARTICLE 7 for purposes of effecting offers or sales of Common Stock of a Blocking Party, pursuant thereto would require, under the Securities Act, premature disclosure in the registration statement (or the prospectus relating thereto) of material, nonpublic information concerning the Blocking Party, its business or prospects or any of its proposed material transactions, (ii) that such premature disclosure would be materially adverse to the Blocking Party, then (x) the Blocking Party may postpone the filing or effectiveness of such registration statement, or (y) suspend the right of the Selling Party to use the registration statement (and the prospectus relating thereto) for purposes of effecting offers or sales of Common Stock of the Blocking Party pursuant thereto. Notwithstanding the foregoing, neither Party shall under any circumstances be entitled to exercise its right to postpone the filing or effectiveness of, or suspend the use of, a registration statement more than two (2) times in any twelve (12) month period, and the aggregate number of days during which the filing or effectiveness of, or the suspension of the use of, the registration statement may be postponed or suspended shall not exceed ninety (90) days in any such (12) month period. Each Party hereby covenants and agrees that it will not sell any Isis Common Stock or Hybridon Common Stock, as the case may be, pursuant to a registration statement filed under this ARTICLE 7 during a period in which the ability to sell thereunder is suspended as set forth in this SECTION 7.4 and will maintain in confidence the fact and content of any notice provided under this SECTION 7.4.

The effectiveness of a registration statement may not be postponed and the rights of a Selling Party to sell shares under a registration statement may not be suspended under this SECTION 7.4 unless the Blocking Party has similarly suspended distribution rights under any other effective registration statement of which it is the registrant (except for registration statements on Form S-8) and has similarly suspended the rights of its officers and directors to trade in its securities for at least the same 90 day period.

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ARTICLE 8

POST EFFECTIVE COVENANTS

8.1 ISIS'S VOTING RESTRICTIONS. Isis agrees that, at all times during the Restriction Period, at any meeting or vote by written consent in lieu thereof of the stockholders of Hybridon, however called, Isis shall cause all outstanding shares of Hybridon Restricted Stock that are beneficially owned by Isis or its Affiliates as of the record date fixed for such meeting or on the date of a vote by written consent to be voted in accordance with and in the same proportion as the votes of the other stockholders of Hybridon, not including abstentions. By way of example, if at Hybridon's annual meeting, stockholders holding at least 70% of the combined voting power of Hybridon's voting securities then outstanding, excluding Isis, vote in favor of a proposal, 10% against and 20% abstain, then Isis shall be required to vote 87.5% of its Hybridon Common Stock in favor of such proposal and 12.5% against.

8.2 HYBRIDON'S VOTING RESTRICTIONS. Hybridon agrees that, at all times during the Restriction Period, at any meeting or vote by written consent in lieu thereof of the stockholders of Isis, however called, Hybridon shall cause all outstanding shares of Isis Restricted Stock that are beneficially owned by Hybridon or its Affiliates as of the record date fixed for such meeting or on the date of a vote by written consent to be voted in accordance with and in the same proportion as the votes of the other stockholders of Isis, not including abstentions. By way of example, if at Isis's annual meeting, stockholders holding at least 70% of the combined voting power of Isis's voting securities then outstanding, excluding Hybridon, vote in favor of a proposal, 10% against and 20% abstain, then Hybridon shall be required to vote 87.5% of its Isis Common Stock in favor of such proposal and 12.5% against.

8.3 RESTRICTIONS ON ISIS'S SALE OF ITS HYBRIDON COMMON STOCK.

During the Restriction Period, Isis may only sell, assign, transfer or otherwise dispose of, or engage in any short selling or hedging transaction in respect of (for purposes of SECTIONS 8.3 and 8.4, "sell"), any of the Hybridon Restricted Stock, whether in a private or public sale, pursuant to the conditions and restrictions in this SECTION 8.3, PROVIDED, HOWEVER, that nothing in this SECTION 8.3 shall prohibit Isis from transferring the Hybridon Restricted Stock to an Affiliate of Isis that has agreed, in writing with Hybridon, to be bound by the terms of this ARTICLE 8. During the Restriction Period, Isis shall not sell in any 180-day period a number of shares of Hybridon Restricted Stock in excess of one percent (1%) of the total outstanding shares of Hybridon Common Stock determined on an as-converted basis (which shall be calculated by adding the total number of shares of Hybridon Common Stock outstanding and the total number of shares of Hybridon Common Stock issuable upon conversion of outstanding convertible securities of Hybridon (excluding options and warrants)); PROVIDED, HOWEVER, that in the event the Hybridon Market Price as of a specified date is less than the Hybridon Minimum Price, then in the following 180 day period, Isis shall be allowed to sell a number of shares of Hybridon Restricted Stock that does not exceed three percent (3%) of the total outstanding shares of Hybridon Common Stock determined on an as-converted basis. For the purposes of this SECTION 8.3, (i) the number of

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outstanding shares of Hybridon Common Stock and the number of outstanding shares of Hybridon Common Stock issuable upon conversion of outstanding convertible securities of Hybridon (excluding options and warrants) shall be the actual numbers at the time if known by Isis or, if not known, the stated numbers of such shares reflected in Hybridon's most recent filing of a Form 10-Q or Form 10-K.

8.4 RESTRICTIONS ON HYBRIDON'S SALE OF ITS ISIS COMMON STOCK.

During the Restriction Period, Hybridon may only sell any of the Isis Restricted Stock, whether in a private or public sale, pursuant to the conditions and restrictions in this SECTION 8.4, PROVIDED, HOWEVER, that nothing in this SECTION 8.4 shall prohibit Hybridon from transferring the Isis Restricted Stock to an Affiliate of Hybridon that has agreed, in writing with Isis, to be bound by the terms of this ARTICLE 8. During the Restriction Period, Hybridon shall not sell in any 180-day period a number of shares of Isis Restricted Stock in excess of one percent (1%) of the total outstanding shares of Isis Common Stock determined on an as-converted basis (which shall be calculated by adding the total number of shares of Isis Common Stock outstanding and the total number of shares of Isis Common Stock issuable upon conversion of outstanding convertible securities of Isis (excluding options and warrants)); provided, however, that in the event the Isis Market Price as of a specified date is less than the Isis Minimum Price for the Isis Tranche Period during which such date occurs, then in the following 180 day period, Hybridon shall be allowed to sell a number of shares of Isis Restricted Stock that does not exceed three percent (3%) of the total outstanding shares of Isis Common Stock determined on an as-converted basis. For the purposes of this SECTION 8.4, the number of outstanding shares of Isis Common Stock and the number of shares of Isis Common Stock issuable upon conversion of outstanding convertible securities of Isis (excluding options and warrants) shall be the actual numbers at the time if known by Hybridon or, if not known, the stated numbers of such shares reflected in Isis's most recent filing of a Form 10-Q or Form 10-K.

8.5 CERTAIN TRANSACTIONS PROHIBITED. Notwithstanding any

provision herein to the contrary, for so long as a Party shall hold Isis Restricted Stock or Hybridon Restricted Stock, as the case may be such Party agrees that it will not and will cause its Affiliates to not: (i) except pursuant to SECTION 2.2 and SECTION 2.3, whichever is applicable, acquire, directly or indirectly, by purchase or otherwise, of record or beneficially, any capital stock of the other Party, any securities of the other Party convertible into capital stock of the other Party (which for purposes of this Master Agreement shall include without limitation convertible notes), or any rights, options or warrants to acquire capital stock of the other Party; (ii) "solicit" proxies with respect to voting securities of the other Party under any circumstances or become a "participant" in any "election contest" relating to the election of directors of the other Party, as such terms are defined in Regulation 14A under the Exchange Act; (iii) deposit any voting securities of the other Party in a voting trust or subject them to a voting agreement or other agreement of similar effect; (iv) initiate, propose or otherwise solicit stockholders of the other Party for the approval of one or more stockholder proposals at any time, or induce or attempt to induce any other person to initiate any stockholder proposal; (v) present, or propose to present, publicly or otherwise, to the other Party, its Board of Directors or its stockholders any proposal or offer for a merger, tender or

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exchange offer or other form of business combination involving the other Party, or effect, propose to effect or cause to occur any of the foregoing; (vi) take any action individually or jointly with any person, corporation, entity or group or assist any person, corporation, entity or group in taking any action such Party could not take individually under the terms of this Master Agreement, or (vii) take any action which would be reasonably likely to require such Party to make a public announcement regarding a possible transaction involving such Party.

8.6 WAIVER OF RESTRICTIONS. Notwithstanding anything to the contrary set forth herein, either Party may, at any time and from time to time, waive in writing any of the conditions or restrictions contained in this ARTICLE 8. Each Party agrees to keep any request for a waiver and the approval or denial thereof confidential under the terms of Section 7.1 of the License Agreement.

8.7 RESERVATION OF SHARES.

(a) BY HYBRIDON. Hybridon will at all times reserve and keep available, solely for issuance and delivery pursuant to this Master Agreement, such number of shares of Hybridon Common Stock equal to the maximum number of shares of Hybridon Restricted Stock as from time to time may be issuable under this Master Agreement assuming the Hybridon Market Price is the Hybridon Minimum Price.

(b) BY ISIS. Isis will at all times reserve and keep available, solely for issuance and delivery pursuant to this Master Agreement, such number of shares of Isis Common Stock equal to the maximum number of shares of Isis Restricted Stock as from time to time may be issuable under this Master Agreement assuming the Isis Market Price is the Isis Minimum Price.

8.8 CHANGE IN CONTROL OF HYBRIDON. In the event of a Change in Control Transaction by Hybridon, then Isis's obligations in SECTIONS 8.1, 8.3 and 8.5 shall terminate and the Hybridon Common Stock restricted pursuant thereto shall be released from such restrictions.

8.9 CHANGE IN CONTROL OF ISIS. In the event of a Change in Control Transaction by Isis, then Hybridon's obligations in SECTIONS 8.2, 8.4 and 8.5 shall terminate and the Isis Common Stock restricted pursuant thereto shall be released from such restrictions.

ARTICLE 9

INDEMNIFICATION AND CONTRIBUTION

9.1 INDEMNIFICATION. The following provisions shall govern the rights and the duties of the Parties in the event a Party seeks indemnity from the other Party under the provisions of either SECTIONS 7.1 or 7.2, or both, as the case may be.

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(a) Each party entitled to indemnification (the "INDEMNIFIED PARTY") shall give notice to the party required to provide indemnification (the "INDEMNIFYING PARTY") promptly after such Indemnified Party has actual knowledge of any claim as to which indemnity may be sought, and shall permit the Indemnifying Party to assume the defense of any such claim or any litigation resulting therefrom; PROVIDED, that counsel for the Indemnifying Party, who shall conduct the defense of such claim or litigation, shall be approved by the Indemnified Party (whose approval shall not be unreasonably withheld); and, PROVIDED, FURTHER, that the failure of any Indemnified Party to give notice as provided herein shall not relieve the Indemnifying Party of its obligations except to the extent that the Indemnifying Party is adversely affected by such failure. The Indemnified Party may participate in such defense at such party's expense; PROVIDED, HOWEVER, that the Indemnifying Party shall pay such expense if representation of such Indemnified Party by the counsel retained by the Indemnifying Party would be inappropriate due to actual or potential conflicting interests between the Indemnified Party and any other party represented by such counsel in such proceeding; PROVIDED FURTHER that in no event shall the Indemnifying Party be required to pay the expenses of more than one law firm per jurisdiction as counsel for the Indemnified Party. The Indemnifying Party also shall be responsible for the expenses of such defense if the Indemnifying Party does not elect to assume such defense. No Indemnifying Party, in the defense of any such claim or litigation shall, except with the consent of each Indemnified Party, consent to entry of any judgment or enter into any settlement which does not include as an unconditional term thereof the giving by the claimant or plaintiff to such Indemnified Party of a release from

all liability in respect of such claim or litigation, and no Indemnified Party shall consent to entry of any judgment or settle such claim or litigation without the prior written consent of the Indemnifying Party which consent shall not be unreasonably withheld.

(b) In order to provide for just and equitable contribution in circumstances in which the indemnification provided for in SECTIONS 7.1 and 7.2 is due in accordance with its terms but for any reason is held to be unavailable to an Indemnified Party in respect to any expenses, losses, claims, damages and liabilities referred to herein, then the Indemnifying Party shall, in lieu of indemnifying such Indemnified Party, contribute to the amount paid or payable by such Indemnified Party as a result of such losses, claims, damages or liabilities to which such Party may be subject in such proportion as is appropriate to reflect the relative fault of the Indemnified Party on the one hand and the Indemnifying Party on the other in connection with the statements or omissions which resulted in such losses, claims, damages or liabilities, as well as any other relevant equitable considerations. The relative fault of the Indemnified Party and the Indemnifying Party shall be determined by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission to state a material fact related to information supplied by the Indemnified Party or the Indemnifying Party and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission. Each Party agrees that it would not be just and equitable if contribution pursuant to this SECTIONS 9.1(b) were determined by pro rata allocation or by any other method of allocation which does not take account of the equitable considerations referred to above. Notwithstanding the provisions of this paragraph, (a) in no case shall any Party be liable or responsible for any

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amount in excess of the net proceeds received by such Party from the offering of the securities of the other Party registered on its behalf under either SECTION 7.1 or 7.2, as the case may be, and (b) the Party filing the registration statement shall be liable and responsible for any amount in excess of such proceeds; PROVIDED, HOWEVER, that no person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Securities Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation. Any Party entitled to contribution will, promptly after receipt of notice of commencement of any action, suit or proceeding against such Party in respect of which a claim for contribution may be made against another Party under this paragraph, notify such Party from whom contribution may be sought, but the omission to so notify such Party from whom contribution may be sought shall not relieve such Party from any other obligation may have thereunder or otherwise under this paragraph except to the extent that such Party is adversely affected by such failure. No Party shall be liable for contribution with respect to any action, suit, proceeding or claim settled without its prior written consent, which consent shall not be unreasonably withheld.

ARTICLE 10

TERM AND EVENTS OF DEFAULT

10.1 TERM. This Master Agreement shall commence upon execution and remain in effect for ten years.

10.2 BREACH OF NONPAYMENT AND FAILURE TO COMPLY WITH ARBITRATION ORDER.

(a) BREACH OF NONPAYMENT. In the event a Party is in breach of any its obligations under either SECTION 2.2 or SECTION 2.3, then the non-breaching Party may give written notice to the breaching Party of such breach. Within ten (10) business days of the receipt by the breaching Party of such written notice, the breaching Party shall cure the breach, 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, and (ii) at the same time, pay to the non-breaching Party the amount of the payment which is not in dispute. Failure to either cure such breach OR take the actions required under subsection (i) or (ii) above, whichever action is applicable, shall be an "EVENT OF DEFAULT".

If part or all of a payment is in dispute hereunder, either Party may submit the dispute to arbitration pursuant to SECTION 11.14, in which case the non-payment of the disputed portion shall not be deemed a breach during the pendency of the arbitration. 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) attorneys' fees

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of the non-breaching Party, the fees of the arbitrator and the costs and expenses of the arbitration, (B) any Lost Profits, and (C) in the case the arbitrator finds that a cash payment was due, an amount equal to interest at a 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.

(b) FAILURE TO COMPLY WITH ARBITRATION ORDER. If an arbitrator has rendered a ruling pursuant to Article VIII of the License Agreement that a Party has materially breached this Master Agreement or the License 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 SECTION 2.2 or 2.3 as contemplated by SECTION 10.2(a) (the "ADVERSE RULING"), and 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 such failure shall be deemed an "EVENT OF DEFAULT".

10.3 REMEDIES UPON AN EVENT OF DEFAULT. Upon the occurrence of an Event of Default and written notice to the defaulting Party, (i) the defaulting Party shall have no further rights under this Master Agreement (except, in the event that the licenses and sublicenses granted by the defaulting Party under the License Agreement remain in effective under SECTION 9.2(d) of the License Agreement, the right to receive Common Stock and cash of the non-defaulting Party pursuant to SECTION 2.2 or 2.3, whichever is applicable and the right to have such stock registered, and the provisions relating thereto under SECTION 7), but shall continue to be liable for all of its obligations under this Master Agreement, including but not limited to the obligation to issue Isis or Hybridon Common Stock or pay cash to the non-defaulting Party pursuant to SECTION 2.2 or 2.3, whichever is applicable, and (ii) the non-defaulting Party shall have no further obligations under this Master Agreement other than its obligation to issue Isis or Hybridon Common Stock or pay cash to the defaulting Party pursuant to SECTION 2.2 or 2.3, whichever is applicable, and the obligations to register such stock and the other obligations under SECTION 7 relating thereto, but shall continue to have all of its rights under this Master Agreement, including but not limited to the right to receive Common Stock and cash of the defaulting Party pursuant to SECTION 2.2 or 2.3, whichever is applicable and the benefits of any voting restrictions and trading restrictions imposed under ARTICLE 8 on the other party, the benefits of any registration provisions under ARTICLE 7 and rights arising out of any breach of representations or warranties or other covenants of the defaulting Party under the Agreement.

10.4 SURVIVAL. The terms and conditions in SECTIONS 7.1(a)(ii), 7.1(c), 7.1(d), 7.2(a)(ii), 7.2(c), 7.2(d) AND 7.4, ARTICLE 9 and SECTIONS 10.2, 10.3 and 11.14 shall survive termination or expiration of this Master Agreement.

10.5 FAILURE TO MAKE MASTER AGREEMENT DELIVERIES. Notwithstanding any provision in this Master Agreement or the License Agreement to the contrary, if Isis breaches Section

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2.3(a)(i) or Article 5 of this Master Agreement, Hybridon shall have the right, at its sole election, effective immediately upon written notice to Isis, to terminate this Master Agreement AB INITIO. The Parties hereby agree that termination of this Master Agreement as provided in this Section 10.5 shall not be the exclusive remedy of Hybridon in the event of a breach of Section 2.3(a)(i) or Article 5 of this Master Agreement by Isis and that, without regard to the arbitration provisions of Article VIII of the License Agreement, Hybridon shall be entitled to declare such breach to be an Event of Default under this Master Agreement and to seek any and all remedies to which Hybridon may be entitled at law or in equity, including without limitation seeking to enforce the provisions of Section 2.3(a)(i) and Article 5 of this Master Agreement (and Section 10.3 of this Master Agreement if the breach is declared by Hybridon to be an Event of Default). In the event of any action by Hybridon under this Section 10.5 for payment under Section 2.3(a)(i) and Article 5 of this Master Agreement or otherwise, Hybridon shall

be entitled to reimbursement of attorney's fees and other collection costs incurred by Hybridon and 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 due commencing on the due date through the date of actual payment.

ARTICLE 11

MISCELLANEOUS PROVISIONS

11.1 ADJUSTMENTS FOR DIVIDENDS, SPLITS, REORGANIZATIONS, RECLASSIFICATIONS, ETC.

(a) If after the date hereof (i) the outstanding shares of the Isis Common Stock or Hybridon Common Stock, as the case may be (for purposes of this SECTION 11.1(a), the "Subject Stock") shall be subdivided or split into a greater number of shares or a dividend in Subject Stock shall be paid in respect of such Subject Stock, (ii) the outstanding shares of Subject Stock are combined, (iii) a Party shall pay a dividend in securities of the Party (other than Subject Stock) or of the property (including cash) on the Subject Stock, or (iv) there shall occur any merger, consolidation, capital reorganization or reclassification in which the Subject Stock is converted or exchanged for securities, cash or other property (other than as part of a Change of Control Transaction), all dollar amounts and share quantities in this Master Agreement, as well as the class or series of stock constituting the Subject Stock, shall be adjusted to reflect such stock splits, stock dividend, combination, other dividend, merger, consolidation, capital reorganization or reclassification consistent with the economic intent of the parties, PROVIDED, HOWEVER, there shall be no adjustments to the amount of any cash payments which either Party may be obligated to make or have the election to make in lieu of the issuance of shares of Subject Stock. After any event referenced in clauses (i) through (iv) is consummated, if applicable, all references herein to Isis Common Stock or Hybridon Common Stock, as the case may be, shall be deemed to refer to the capital stock or property (including cash) into or for which the Subject Stock was converted or exchanged, with the necessary changes in detail. All calculations under this SECTION 11.1 shall be made to the nearest cent or whole number amount for shares.

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(b) Upon the happening of any event referenced in clauses (i) through (iv) in SECTION 11.1(a), the Party whose Common Stocks is so affected shall forthwith give written notice thereof to the other Party stating the adjusted figures and setting forth in reasonable detail the method of calculation and the facts upon which such calculation is based.

11.2 SUCCESSORS AND ASSIGNS. This Master Agreement shall be binding upon and inure to the benefit of the Parties and their respective successors and assigns, except that neither Party may assign its respective obligations hereunder, including an assignment by merger or by operation of law, without the prior written consent of the other Party, unless such assignment is in connection with the sale or transfer of all or substantially all of the business or assets of the assigning Party. Any attempted assignment in contravention of this provision shall be void.

11.3 NOTICES. All notices, requests, consents and other communications hereunder shall be in writing and shall be delivered by hand, by facsimile, or by certified mail, postage prepaid, return receipt requested:

(a) If to Hybridon, at the address set forth below:

Hybridon, Inc.
345 Vassar Street
Cambridge, MA 02139
Attention: President
Telephone: 617-679-5500
Facsimile: 617-679-5592

WITH A COPY TO:

James Pollock, Esq.
Holland & Knight, LLP
10 St. James Avenue
Boston, MA 02116
Telephone: (617) 523-2700
Facsimile: (617) 523-6850

(b) If to Isis:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Attention: President
Telephone: (760) 931-9200
Facsimile: (760) 931-96391

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WITH A COPY TO:

L. Kay Chandler, Esq.
Cooley Godward LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121
Telephone: (858) 550-6000
Facsimile: (858) 453-3555

Any notice or other communication so addressed and so delivered shall be deemed to have been received on the date of hand delivery or facsimile or, if sent by certified mail, return receipt requested, on the date of mailing.

11.4 ENTIRE AGREEMENT; ATTACHMENTS.

(a) This Master Agreement and all exhibits hereto, together with the Transaction Documents, represent the entire understanding and agreement between the Parties with respect to the subject matter hereof and supersede all prior oral and written and all contemporaneous oral negotiations, commitments and understandings between the Parties.

(b) If the provisions of the License Agreement are inconsistent with the provisions of this Master Agreement, the provisions of the License Agreement shall prevail. The Exhibits are hereby incorporated as integral parts of this Master Agreement.

11.5 SEVERABILITY. Any provision of this Master Agreement which is invalid, illegal or unenforceable in any jurisdiction shall, as to that jurisdiction, be ineffective to the extent of such invalidity, illegality or unenforceability, without affecting in any way the remaining provisions hereof in such jurisdiction or rendering that or any other provision of this Master Agreement invalid, illegal or unenforceable in any other jurisdiction. The language in this Master Agreement is acknowledged by the Parties to be language chosen by the Parties to express their mutual consent, and no rule of strict construction against any Party shall apply to any term or provision hereof.

11.6 INVESTIGATION OF THE PARTIES. All representations and warranties contained herein which are made to the best knowledge of a Party shall require that such Party investigate and inquire with respect thereto to the extent that a reasonable business person would make such investigation and inquiry in light of the circumstances at the time, without regard to this transaction.

11.7 EXPENSES. Except as otherwise expressly provided herein, Hybridon, on the one hand, and Isis on the other hand, will pay all fees and expenses (including, without limitation, legal and accounting fees and expenses) incurred by them in connection with the transactions contemplated hereby.

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11.8 GOVERNING LAW. This Master Agreement shall be governed by and construed in accordance with the laws of the State of Delaware, without regard to the conflict of laws rules of any jurisdiction.

11.9 SECTION HEADINGS. The section headings are for the convenience of the Parties and in no way alter, modify, amend, limit, or restrict the contractual obligations of the Parties.

11.10 COUNTERPARTS. This Master Agreement may be executed in one or more counterparts, each of which shall be deemed to be an original, but all of which shall be one and the same document. A copy or facsimile of a signature shall be binding upon the signatory as if it were an original signature.

11.11 WAIVER AND MODIFICATION. A Party may only waive the failure of another Party to comply with any of such Party's obligations, agreements or conditions as set forth herein expressly in writing. To the extent permitted by law, this Master Agreement may be amended or modified in whole or in part by an agreement in writing executed on behalf of the Parties at any time.

11.12 NO WAIVER. No failure on the part of any Party to exercise, and no delay in exercising (except where a specific time period is specified) any right shall operate as a waiver thereof, nor shall any single or partial exercise by any Party of any right preclude any other future exercise thereof or the exercise of any other right. No investigation, review or audit by either party of the other prior to or after the date hereof shall stop or prevent either Party from exercising any right hereunder or be deemed to be a waiver of any such right.

11.13 FURTHER ASSURANCES. At any time and from time to time after the Effective Date, each party shall promptly execute and deliver such instruments of transfer, conveyance, assignment and confirmation, and take all such other action as the other Party may reasonably request to carry out the purpose and intent of this Master Agreement.

11.14 DISPUTE RESOLUTION.

(a) Any Party must submit any dispute under this Master Agreement to arbitration pursuant to the terms and conditions set forth in Article VII of the License Agreement.

(b) Nothing in this SECTION 11.14 shall prevent either Party from seeking from a court of competent jurisdiction a preliminary injunction, temporary restraining order or similar relief in order to prevent or limit an irreparable harm that may occur in the absence thereof.

11.15 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.

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11.16 CONFIDENTIALITY. The Parties hereto agree that the provisions of the License Agreement relating to confidentiality are incorporated herein by reference.

[Remainder of page intentionally omitted]

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IN WITNESS WHEREOF, the parties hereto have caused this Master Agreement to be executed as of the date first written above.

HYBRIDON, INC.

By: /s/ Sudhir Agrawal

Title: President & CSO

By: /s/ R. Andersen

Title: CFO

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

Title: Exective Vice President

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EXHIBIT A

LICENSE AGREEMENT

COLLABORATION AND LICENSE AGREEMENT

BY AND BETWEEN

ISIS PHARMACEUTICALS, INC.

AND

HYBRIDON, INC.

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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 hybridizes 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

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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.

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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,

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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

* Confidential Treatment Requested - 4 -

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, Funderon 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

*Confidential Treatment Requested - 5 -

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

Section 1.18 [*]

*Confidential Treatment Requested - 6 -

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

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

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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

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

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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 1.30 "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 1.31 "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 1.32 "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 1.33 "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 1.34 "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 1.35 "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.

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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

- (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 Funderon 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

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

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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

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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

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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

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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

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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

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

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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

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

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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

(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

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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

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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

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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

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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;

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(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

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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

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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) EpiGenesis' 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

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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

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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

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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.

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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

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

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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.

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(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.

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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

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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

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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.

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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.

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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

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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

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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]

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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

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

[*]

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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).