

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

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

Date of report (Date of earliest event reported): January 24, 2007 (January 17, 2006)

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware

(State or Other Jurisdiction of Incorporation)

000-19125

(Commission File No.)

33-0336973

(IRS Employer Identification No.)

1896 Rutherford Road

Carlsbad, CA 92008

(Address of Principal Executive Offices and Zip Code)

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

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 1.01. Entry into a Material Definitive Agreement.

On January 17, 2007, Isis Pharmaceuticals, Inc. (the "Company") entered into a Purchase Agreement (the "Purchase Agreement") with Lehman Brothers Inc., Cowen and Company, LLC, Leerink Swann & Co., Inc. and Needham & Company, LLC (collectively, the "Initial Purchasers"), relating to the issuance and sale by the Company to the Initial Purchasers of \$125 million in aggregate principal amount of its 2 5/8% Convertible Subordinated Notes due 2027 (the "Notes"). The Company granted the Initial Purchasers an option to purchase up to an additional \$37.5 million in aggregate principal amount of Notes to cover over-allotments, if any, which the Initial Purchasers exercised in full on January 22, 2007. As a result, on January 23, 2007 the Company issued and sold to the Initial Purchasers \$162.5 million in aggregate principal amount of Notes.

The Notes were offered and sold to qualified institutional buyers pursuant to Rule 144A under the Securities Act of 1933, as amended (the "Securities Act"). None of the Notes (including any shares of common stock issuable upon conversion thereof) have been registered under the Securities Act or under any state securities laws and, unless so registered, may not be offered or sold in the United States or to U.S. persons except pursuant to an exemption from, or in a transaction not subject to the registration requirements of the Securities Act and applicable state securities laws. This report does not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall it constitute an offer, solicitation or sale in any jurisdiction in which such offer, solicitation or sale is unlawful.

The Company intends to use the net proceeds of this offering, which were approximately \$157.6 million, to repurchase, retire or repay its existing 5 1/2% Convertible Subordinated Notes due 2009 ("Existing Convertible Notes"), of which \$125.0 million is currently outstanding. Through privately negotiated transactions, the Company has already agreed to repurchase approximately \$44.1 million aggregate principal amount of the total outstanding Existing Convertible Notes and plans to settle these repurchase transactions on January 24, 2007. In addition, the Company intends to use net proceeds remaining after the repurchase, retirement or repayment, for general corporate and working capital purposes.

The Notes were issued pursuant to an Indenture, dated January 23, 2007 (the "Indenture"), between the Company and Wells Fargo Bank, N.A., a national banking association, as trustee.

The Notes are the Company's unsecured subordinated obligations and are subordinated in right of payment to all existing and future senior secured indebtedness.

The Notes are convertible under certain circumstances into shares of the Company's common stock at a conversion rate of 68.3761 shares per \$1,000 of principal amount of Notes, subject to adjustment in certain circumstances. This conversion rate is equivalent to a conversion price of approximately \$14.63 per share, which represents a 30.0% premium over the closing price per share of the Company's common stock on January 17, 2007.

The Notes are redeemable at Isis' option on or after February 15, 2012 at a redemption price equal to the percentage of principal amount described below plus accrued and unpaid interest:

- if redeemed between February 15, 2012 and February 14, 2013, 100.75%;
- if redeemed between February 15, 2013 and February 14, 2014, 100.375%; and
- if redeemed on or after February 15, 2014, 100.0%.

In addition, the Notes are subject to repurchase at the option of holders on February 15, 2014, February 15, 2017 and February 15, 2022, and upon the occurrence of certain defined conditions, at 100.0% of the principal amount of the Notes being repurchased plus accrued interest and unpaid interest.

Upon the occurrence of specific fundamental changes, the holders of the Notes will have the right, subject to various conditions and restrictions, to require the Company to repurchase the Notes, in whole or in part, at par plus accrued and unpaid interest. In addition, subject to certain exceptions, if the Company undergoes certain specific fundamental changes, the Company will pay a make whole premium by adjusting the conversion rate on the Notes converted in connection with such fundamental change.

If an event of default on the Notes occurs, the principal amount of the Notes, plus accrued and unpaid interest, may be declared immediately due and payable, subject to certain conditions set forth in the Indenture.

The following will be events of default under the Indenture:

- the Company fails to pay any interest on the Notes when due and such failure continues for a period of 30 calendar days;
- the Company fails to pay principal of the Notes when due at maturity;
- the Company fails to pay the redemption price when due;
- the Company fails to deliver common stock, or cash in lieu thereof, or a combination of the foregoing, upon the conversion of any Notes and such failure continues for 15 days;
- the Company fails to provide notice of the anticipated effective date or actual effective date of a fundamental change on a timely basis as required in the Indenture;
- the Company fails to perform or observe any other term, covenant or agreement in the Notes or the indenture for a period of 60 calendar days after written notice of such failure; or
- certain events involving the Company's bankruptcy, insolvency or reorganization or the bankruptcy, insolvency or reorganization of any of the Company's wholly-owned significant subsidiaries.

In connection with the sale of the Notes, the Company entered into a Registration Rights Agreement, dated January 23, 2006 (the "Registration Rights Agreement"), with the Initial Purchasers. Under the Registration Rights Agreement, the Company agreed to file with the Securities and Exchange Commission a shelf registration statement for the resale of the Notes and the sale of the shares of common stock issuable upon conversion of the Notes within 90 calendar days of the date of issuance of the Notes. The Company also agreed to use its reasonable best efforts to cause such shelf registration statement to be declared effective within 180 calendar days of such issuance date. In the event that the Company fails to satisfy certain

of its obligations under the Registration Rights Agreement, it will be required to pay additional interest to the holders of the Notes.

The descriptions of the Purchase Agreement, the Indenture and the Registration Rights Agreement, set forth above are qualified in their entirety by reference to the full and complete terms set forth in such agreements, copies of which are filed as exhibits to this Current Report on Form 8-K and incorporated by reference herein.

Item 2.03. Creation of a Direct Financial Obligation or an Obligation Under an Off-Balance Sheet Arrangement of a Registrant.

The disclosure set forth above under Item 1.01. is hereby incorporated by reference in this Item 2.03.

Item 3.02. Unregistered Sales of Equity Securities.

The disclosure set forth above under Item 1.01. is hereby incorporated by reference in this Item 3.02.

Item 8.01. Other Events.

On January 24, 2007 the Company issued a press release announcing the closing of this transaction. A copy of this press release is attached hereto as Exhibit 99.1.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

- 4.1 Indenture, dated January 23, 2007, between the Company and Wells Fargo Bank, N.A., a national banking association, as trustee, including Form of 2 5/8% Convertible Senior Note due 2027.
 - 4.2 Registration Rights Agreement, dated January 23, 2007, among the Company and the Initial Purchasers identified therein.
 - 10.1 Purchase Agreement, dated January 17, 2007, among the Company and the Initial Purchasers identified therein.
 - 99.1 Press release dated January 24, 2007.
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SIGNATURE

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

Isis Pharmaceuticals, Inc.

Dated: January 23, 2007

By: /s/ B. Lynne Parshall

B. Lynne Parshall

Executive Vice President,

Chief Financial Officer and Director

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ISIS PHARMACEUTICALS, INC.

2⁵/₈ % Convertible Subordinated Notes due 2027

INDENTURE

Dated as of January 23, 2007

WELLS FARGO BANK, N.A.

Trustee

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Exhibit A	—	Form of Note
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INDENTURE dated as of January 23, 2007, among ISIS PHARMACEUTICALS, INC., a Delaware corporation (the “**Company**”), WELLS FARGO BANK, N.A., a national banking association, as trustee (the “**Trustee**”).

WHEREAS, the Company has duly authorized the creation of an issue of its 2⁵/₈ % Convertible Subordinated Notes due 2027 (the “**Notes**”), having the terms, tenor, amount and other provisions hereinafter set forth, and, to provide therefor, the Company has duly authorized the execution and delivery of

this Indenture; and

WHEREAS, all things necessary to make the Notes, when the Notes are duly executed by the Company and authenticated and delivered hereunder and duly issued by the Company, the valid obligations of the Company, and when the Notes are duly executed by the Company and authenticated and delivered hereunder and duly issued by the Company, and to make this Indenture a valid and binding agreement of the Company, in accordance with their and its terms, have been done and performed, and the execution of this Indenture and the issue hereunder of the Notes have in all respects been duly authorized,

NOW, THEREFORE, THIS INDENTURE WITNESSETH:

For and in consideration of the premises and the purchase of the Securities by the holders thereof, it is mutually covenanted and agreed, for the equal and proportionate benefit of all Noteholders, as follows:

ARTICLE 1

DEFINITIONS AND INCORPORATION BY REFERENCE

SECTION 1.01. Definitions.

“Additional Interest” has the meaning specified for Additional Interest in Section 3(a) of the Registration Rights Agreement.

“Additional Interest Notice” has the meaning specified in Section 4.08.

“Additional Notes” has the meaning set specified in Section 2.01.

“Additional Shares” has the meaning specified in Section 10.04(b).

“Affiliate” of any specified Person means any other Person, directly or indirectly, controlling or controlled by or under direct or indirect common control with such specified Person. For the purposes of this definition, “control” when used with respect to any Person means the power to direct the management and policies of such Person, directly or indirectly, whether through the ownership of voting securities, by contract or otherwise; and the terms “controlling” and “controlled” have meanings correlative to the foregoing.

“Agent Members” has the meaning specified in Section 2.08(b)(vi).

“Applicable Consideration” has the meaning specified in Section 10.06(c).

“Bank Indebtedness” means any now existing or hereafter arising obligations for borrowed money, cash management services, reimbursement obligations under letters of credit, depositary arrangements and similar ancillary services in favor of Silicon Valley Bank, including all amounts payable under or in respect of that certain Loan and Security Agreement, dated December 15, 2003, between the Company and Silicon Valley Bank, including the related negative pledge agreement, as each such obligation and the documents evidencing the same may be amended, restated, supplemented, waived, refinanced, replaced, renewed, extended or otherwise modified from time to time, including principal, premium (if any), interest (including interest accruing on or after the filing of any petition in bankruptcy or for reorganization relating to the Company whether or not a claim for post-filing interest is allowed in such proceedings), fees, charges, expenses, reimbursement obligations, Guarantees, indemnities and all other amounts payable thereunder or in respect thereof.

“Bankruptcy Law” has the meaning specified in Section 6.01.

“Board of Directors” means the Board of Directors of the Company or, other than in the case of the definition of “Continuing Directors” and “Fundamental Change,” any committee thereof duly authorized to act on behalf of such Board.

“Business Day” means each day which is not a Legal Holiday.

“Capital Stock” of any Person means any and all shares, interests, rights to purchase, warrants, options, participations or other equivalents of or interests in (however designated) equity of such Person, including any Preferred Stock, but excluding any debt securities convertible into such equity.

“Cash Amount” has the meaning specified in Section 10.12.

“Cash Equivalent” means (a) marketable direct obligations issued or unconditionally guaranteed by the United States or any agency or any State thereof having maturities of not more than one (1) year from the date of acquisition; (b) commercial paper maturing no more than one (1) year after its creation and having the highest rating from either Standard & Poor’s Ratings Group or Moody’s Investors Service, Inc., (c) bank’s certificates of deposit issued maturing no more than one (1) year after issue; and (d) money market funds at least ninety-five percent (95%) of the assets of which constitute Cash Equivalents of the kinds described in clauses (a) through (c) of this definition.

“Closing Sale Price” of any share of Common Stock or any other security on any Trading Day means the closing sale price of such security (or, if no closing sale price is reported, the average of the closing bid and closing ask prices or, if more than one in either case, the average of the average closing bid and the average closing ask prices) on such date as reported in composite transactions for the principal U.S. securities exchange on which the shares of Common Stock or other security are traded or, if the shares of Common Stock or other security are not listed on a U.S. national or regional securities exchange, as reported by the Nasdaq Stock Market or by Pink Sheets LLC. In the absence of such a quotation, the Closing Sale Price shall be determined by a nationally recognized securities dealer retained by the Company for that

purpose. The Closing Sale Price shall be determined without reference to extended or after hours trading.

“Closing Date” means the date of this Indenture.

“Code” means the Internal Revenue Code of 1986, as amended.

“Common Stock” means any stock of any class of the Company which has no preference in respect of dividends or of amounts payable in the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company and which is not subject to redemption by the Company. Subject to the provisions of Section 10.06, however, shares issuable on conversion of Notes shall include only shares of the class designated as common stock of the Company at the date of this Indenture (namely, the Common Stock, par value \$0.01) or shares of any class or classes resulting from any reclassification or reclassifications thereof and which have no preference in respect of dividends or of amounts payable in the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company and which are not subject to redemption by the Company; provided that if at any time there shall be more than one such resulting class, the shares of each such class then so issuable on conversion shall be substantially in the proportion which the total number of shares of such class resulting from all such reclassifications bears to the total number of shares of all such classes resulting from all such reclassifications.

“Company” means the party named as such in this Indenture until a successor replaces it and, thereafter, means the successor and, for purposes of any provision contained herein and required by the TIA, each other obligor on the indenture securities.

“Company Repurchase Notice” has the meaning specified in Section 3.06.

“Continuing Directors” means, as of any date of determination, any member of the Board of Directors who (i) was a member of the Board of Directors on the date of this Indenture; or (ii) was nominated for election or elected to the Board of Directors with the approval of a majority of the Continuing Directors who were members of the Board of Directors at the time of such new director’s nomination or election.

“Conversion Date” has the meaning specified in Section 10.02.

“Conversion Notice” has the meaning specified in Section 10.02.

“Conversion Period” means the 20-Trading Day period (i) if the Company has called the Notes delivered for conversion for redemption, ending on the third Trading Day immediately preceding the redemption date, (ii) with respect to conversions in connection with a Fundamental Change, ending on the third Trading Day prior to the Repurchase Date relating to such Fundamental Change, (iii) with respect to Conversion Notices received during the period beginning 25 Trading Days preceding the Maturity Date and ending one Trading Day preceding the Maturity Date, ending on the third Trading Day immediately preceding the Maturity Date, (iv) if the Company has irrevocably elected to make a cash payment of Principal upon conversion, beginning on the third Trading Day following the Company’s receipt of the

Conversion Notice and (v) in all other cases, beginning on the Trading Day following the final Trading Day of the Conversion Retraction Period.

“Conversion Price” on any date of determination means \$1,000 divided by the Conversion Rate in effect on that date.

“Conversion Rate” means the number of shares of Common Stock into which each \$1,000 principal amount of Notes is convertible, which is initially 68.3761, subject to adjustments as set forth herein.

“Conversion Retraction Period” means the two-Trading Day period beginning on the Trading Day after the Company notifies the Trustee of the method of settlement for the conversion of Notes.

“Conversion Value” has the meaning specified in Section 10.12.

“Corporate Trust Office” or other similar term, means the designated office of the Trustee at which at any particular time its corporate trust business as it relates to this Indenture shall be administered, which office is, at the date as of which this Indenture is dated, located at Wells Fargo Bank, N.A., Corporate Trust Services, 608 2nd Avenue South, MAC N9303-120, Minneapolis, MN 55479, Attention: Isis Pharmaceuticals Account Manager or at any other time at such other address as the Trustee may designate from time to time by notice to the Company.

“Current Market Price” has the meaning specified in Section 10.05(g)(i).

“Custodian” has the meaning specified in Section 6.01.

“Daily Conversion Value” has the meaning specified in Section 10.12.

“Default” means any event which is, or after notice or passage of time or both would be, an Event of Default.

“Depository” means the clearing agency registered under the Exchange Act that is designated to act as the Depository for the Global Notes. DTC shall be the initial Depository, until a successor shall have been appointed and become such pursuant to the applicable provisions of this Indenture, and thereafter, “Depository” shall mean or include such successor.

“Designated Senior Indebtedness” means (i) the Bank Indebtedness and (ii) the Company’s obligations under any other particular Senior Indebtedness with respect to which the instrument creating or evidencing the same or the assumption or Guarantee thereof (or related agreements or documents to which the Company is a party) expressly provides that such Senior Indebtedness shall be “designated Senior indebtedness” for the purposes of this Indenture (provided that such instrument, agreement or other document may place limitations and conditions on the right of such Senior Indebtedness to exercise the rights of Designated Senior Indebtedness).

“Determination Date” has the meaning specified in Section 10.05(k).

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“Distributed Assets” has the meaning specified in Section 10.05(d).

“Distribution Notice” has the meaning specified in Section 10.01(c).

“DTC” means The Depository Trust Company.

“Effective Date” has the meaning specified in Section 10.04(b).

“Event of Default” has the meaning specified in Section 6.01.

“Exchange Act” means the Securities Exchange Act of 1934, as amended.

“Expiration Time” has the meaning specified in Section 10.05(f).

“Fair Market Value” has the meaning specified in Section 10.05(g)(ii).

“Fiscal Quarter” means, with respect to the Company, the fiscal quarter publicly disclosed by the Company. The Company shall confirm the ending dates of its fiscal quarters for the current fiscal year to the Trustee upon the Trustee’s request.

“Fundamental Change” means the occurrence of any of the following after the original issuance of the Notes:

- (a) the consummation of any transaction (including, without limitation, any merger or consolidation) the result of which is that any “person” acquires more than 50% of the Company’s Capital Stock that is at the time entitled to vote by the holder thereof in the election of the Board of Directors (or comparable body);
- (b) the first day on which a majority of the members of the Board of Directors are not Continuing Directors;
- (c) the adoption of a plan relating to the liquidation or dissolution of the Company;
- (d) the consolidation or merger of the Company with or into any other Person, or the sale, lease, transfer, conveyance or other disposition, in one or a series of related transactions, of all or substantially all of the Company’s assets and those of its subsidiaries taken as a whole to any “person” (as this term is used in Section 13(d)(3) of the Exchange Act), other than:
 - (i) any transaction:
 - (A) that does not result in any reclassification, conversion, exchange or cancellation of outstanding shares of the Company’s Capital Stock; and
 - (B) pursuant to which the holders of 50% or more of the total voting power of all shares of the Company’s Capital Stock entitled to vote generally in elections of directors of the Company immediately prior to

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such transaction have the right to exercise, directly or indirectly, 50% or more of the total voting power of all shares of the Company’s Capital Stock entitled to vote generally in elections of directors of the continuing or surviving Person immediately after giving effect to such transaction; or

(ii) any merger primarily for the purpose of changing the Company’s jurisdiction of incorporation and resulting in a reclassification, conversion or exchange of outstanding shares of Common Stock solely into shares of common stock of the surviving entity; or

(e) the termination of trading of the Common Stock, which will be deemed to have occurred if the Common Stock or other common stock into which the Notes are convertible is neither listed for trading on a United States national securities exchange nor approved for listing on the Nasdaq Global Select Market or the Nasdaq Global Market or any similar United States system of automated dissemination of quotations of securities prices, and no American Depositary Shares or similar instruments for such common stock are so listed or approved for listing in the United States.

However, a Fundamental Change will be deemed not to have occurred if more than 90% of the consideration in the transaction or transactions (other than cash payments for fractional shares and cash payments made in respect of dissenters’ appraisal rights) which otherwise would constitute a Fundamental Change under clauses (a) or (d) above consists of shares of Common Stock, depositary receipts or other certificates representing common equity interests traded or to be traded immediately following such transaction on a U.S. national securities exchange or quoted on the Nasdaq Global Select Market or the Nasdaq Global Market and, as a result of the transaction or transactions, the Notes become convertible solely into such common stock, depositary receipts or other certificates representing common equity interests (and any rights attached thereto) and other Applicable Consideration.

“Fundamental Change Repurchase Date” has the meaning specified in Section 3.04(a).

“GAAP” means generally accepted accounting principles in the United States of America as in effect on the Closing Date, including those set forth in (i) the opinions and pronouncements of the Accounting Principles Board of the American Institute of Certified Public Accountants, (ii) statements and pronouncements of the Financial Accounting Standards Board, (iii) such other statements by such other entity as approved by a significant segment of the accounting profession, and (iv) the rules and regulations of the SEC governing the inclusion of financial statements (including pro forma financial statements) in periodic reports required to be filed pursuant to Section 13 of the Exchange Act, including opinions and pronouncements in staff accounting bulletins and similar written statements from the accounting staff of the SEC. All ratios and computations based on GAAP contained in this Indenture shall be computed in conformity with GAAP.

“Global Notes” has the meaning specified in Section 2.02.

“Guarantee” means any obligation, contingent or otherwise, of any Person directly or indirectly guaranteeing any Indebtedness of any other Person and any obligation, direct or

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indirect, contingent or otherwise, of such Person (i) to purchase or pay (or advance or supply funds for the purchase or payment of) such Indebtedness of such other Person (whether arising by virtue of partnership arrangements, or by agreement to keep-well, to purchase assets, goods, securities or services, to take-or-pay, or to maintain financial statement conditions or otherwise) or (ii) entered into for purposes of assuring in any other manner the obligee of such Indebtedness of the payment thereof or to protect such obligee against loss in respect thereof (in whole or in part); provided, however, that the term “Guarantee” shall not include endorsements for collection or deposit in the ordinary course of business. The term “Guarantee” used as a verb has a corresponding meaning. The term “Guarantor” shall mean any Person Guaranteeing any obligation.

“Incur” means create, issue, assume, Guarantee, incur, or otherwise become liable for; provided, however, that any Indebtedness or Capital Stock of a Person existing at the time such Person becomes a Subsidiary (whether by merger, consolidation, acquisition or otherwise) shall be deemed to be Incurred by such Person at the time it becomes a Subsidiary. The term “Incurrence” when used as a noun shall have a correlative meaning. The accretion of principal of a non-interest bearing or other discount security shall not be deemed the Incurrence of Indebtedness.

“Indebtedness” means, means, with respect to any Person, and without duplication:

(i) all indebtedness, obligations and other liabilities (contingent or otherwise) of such Person for borrowed money (including obligations in respect of overdrafts, foreign exchange contracts, currency exchange agreements, interest rate protection agreements, and any loans or advances from banks, whether or not evidenced by notes or similar instruments) or evidenced by bonds, debentures, notes or similar instruments (whether or not the recourse of the lender is to the whole of the assets of such Person or to only a portion thereof), other than any account payable or other accrued current liability or obligation incurred in the ordinary course of business in connection with the obtaining of materials or services;

(ii) all reimbursement obligations and other liabilities (contingent or otherwise) of such Person with respect to letters of credit, bank guarantees or bankers’ acceptances;

(iii) all obligations and liabilities (contingent or otherwise) in respect of leases of such Person required, in conformity with GAAP, to be accounted for as capitalized lease obligations on the balance sheet of such Person and all obligations and other liabilities (contingent or otherwise) under any lease or related document (including a purchase agreement) in connection with the lease of real property which provides that such Person is contractually obligated to purchase or cause a third party to purchase the leased property and thereby guarantee a minimum residual value of the leased property to the lessor and the obligations of such Person under such lease or related document to purchase or to cause a third party to purchase such leased property;

(iv) all obligations of such Person (contingent or otherwise) with respect to an interest rate or other swap, cap or collar agreement or other similar instrument or

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agreement or foreign currency hedge, exchange, purchase or similar instrument or agreement;

(v) all direct or indirect guaranties or similar agreements by such Person in respect of, and obligations or liabilities (contingent or otherwise) of such Person to purchase or otherwise acquire or otherwise assure a creditor against loss in respect of, indebtedness, obligations or liabilities of another person of the kind described in clauses (i) through (iv);

(vi) any indebtedness or other obligations described in clauses (i) through (v) secured by any mortgage, pledge, lien or other encumbrance existing on property which is owned or held by such Person, regardless of whether the indebtedness or other obligation secured thereby shall have been assumed by such Person; and

(vi) any and all deferrals, renewals, extensions and refundings of, or amendments, modifications or supplements to, any indebtedness, obligation or liability of the kind described in clauses (i) through (vi).

“Indenture” means this Indenture as amended or supplemented from time to time.

“Initial Notes” has the meaning specified in Section 2.01.

“Initial Purchasers” means Lehman Brothers Inc., Cowen and Company LLC, Needham & Company, LLC and Leerink Swann & Co., Inc. (each, an “Initial Purchaser”).

“interest” means, when used with reference to the Notes, any interest payable under the terms of the Notes, including defaulted interest, Special Interest, if any, and Additional Interest, if any, payable under the terms of the Registration Rights Agreement.

“Legal Holiday” has the meaning specified in Section 13.08.

“Market Disruption Event” means the occurrence or existence during the one-half hour period ending on the scheduled close of trading on any Trading Day for the Common Stock of any material suspension or limitation imposed on trading (by reason of movements in price exceeding limits permitted by the stock exchange or otherwise) in the Common Stock or in any options, contracts or future contracts relating to the Common Stock.

“Maturity Date” means February 15, 2027.

“Non-Payment Default” has the meaning specified in Section 12.03.

“Non-Stock Change of Control” means a transaction described under clause (a) or clause (d) in the definition of Fundamental Change pursuant to which 10% or more of the consideration for Common Stock (other than cash payments for fractional shares, if applicable, and cash payments made in respect of dissenters’ appraisal rights) in such transaction consists of cash or securities (or other property) that are not shares of Common Stock, depositary receipts or other certificates representing common equity interests traded or scheduled to be traded immediately

following such transaction on a U.S. national securities exchange or quoted on the Nasdaq Global Select Market or the Nasdaq Global Market.

“Notes” means any Notes issued, authenticated and delivered under this Indenture, including the Initial Notes and any Global Notes, and where applicable, the Additional Notes.

“Noteholder” or “Holder” means the Person in whose name a Note is registered on the Registrar’s books.

“Officer” means the Chairman of the Board, the Chief Executive Officer, the Chief Financial Officer, the President, any Vice President, the Treasurer or the Secretary of the Company.

“Officer’s Certificate” means a certificate signed by any Officer.

“Opinion of Counsel” means a written opinion, subject to customary assumptions and exceptions, from legal counsel who is reasonably acceptable to the Trustee. The counsel may be an employee of or counsel to the Company or the Trustee.

“Paying Agent” has the meaning specified in Section 2.05.

“Payment Blockage Notice” has the meaning specified in Section 12.03.

“Payment Blockage Period” has the meaning specified in Section 12.03.

“Payment Default” has the meaning specified in Section 12.03.

“Person” means any individual, corporation, partnership, limited liability company, joint venture, association, joint-stock company, trust, unincorporated organization, government or any agency or political subdivision thereof or any other entity.

“PORTAL Market” means The PORTAL Market operated by the Nasdaq Stock Market or any successor thereto.

“Preferred Stock”, as applied to the Capital Stock of any Person, means Capital Stock of any class or classes (however designated) that is preferred as to the payment of dividends, or as to the distribution of assets upon any voluntary or involuntary liquidation or dissolution of such Person, over shares of Capital Stock of any other class of such Person.

“Principal” of a Note means the principal of the Note plus the premium, if any, payable on the Note that is due or overdue or is to become due at the relevant time.

“protected purchaser” has the meaning specified in Section 2.09.

“Public Acquirer Change of Control” means a Non-Stock Change of Control in which the acquirer has a class of common stock traded on a U.S. national securities exchange or listed on the Nasdaq Global Select Market or the Nasdaq Global Market or that shall be so traded or quoted when issued or exchanged in connection with such Non-Stock Change of Control (the

“Public Acquirer Common Stock”). If an acquirer does not itself have a class of common stock satisfying the foregoing requirement, it shall be deemed to have Public Acquirer Common Stock if a corporation that directly or indirectly owns at least a majority of the acquirer has a class of common stock satisfying the foregoing requirement, provided that such majority-owning corporation fully and unconditionally guarantees the Notes, in which case all references to Public Acquirer Common Stock shall refer to such class of common stock. “Majority-owned” for these purposes means having “beneficial ownership” (as defined in Rule 13d-3 under the Exchange Act) of more than 50% of the total voting power of all shares of the respective entity’s capital stock that are entitled to vote generally in the election of directors.

“Public Acquirer Common Stock” has the meaning specified in the definition of Public Acquirer Change of Control.

“Purchase Agreement” means the Purchase Agreement, dated January 23, 2007, between the Company and Lehman Brothers Inc., as representative of the Initial Purchasers, relating to the offering and sale of the Notes.

“Purchased Shares” has the meaning specified in Section 10.05(f).

“Record Date” means, with respect to any interest payment date of the Notes, the February 1 and August 1 preceding the applicable February 15 and August 15 interest payment date, respectively. The “record date,” with respect to the Conversion Rate adjustment as provided in Section 10.05, has the meaning specified in Section 10.05(g)(iii).

“Reference Period” has the meaning specified in Section 10.05(d).

“Register” has the meaning specified in Section 2.05.

“Registrar” has the meaning specified in Section 2.05.

“Registration Rights Agreement” means the Registration Rights Agreement, dated as of January 23, 2007, by and between the Company and Lehman Brothers Inc., as representative of the Initial Purchasers, as amended from time to time in accordance with its terms.

“Representative” means Silicon Valley Bank with respect to the Bank Indebtedness and with respect to other Senior Indebtedness means the trustee, agent or representative (if any) for such issue of Senior Indebtedness of the Company.

“Repurchase Date” has the meaning specified in Section 3.05(a).

“Repurchase Notice” has the meaning specified in Section 3.04(c).

“Restricted Securities” has the meaning specified in Section 2.08(c).

“Rule 144A” means Rule 144A as promulgated under the Securities Act as it may be amended from time to time hereafter.

“SEC” means the Securities and Exchange Commission.

“Securities Act” means the Securities Act of 1933, as amended, and the rules and regulations promulgated thereunder, as in effect from time to time.

“Senior Indebtedness” means the principal of, premium, if any, interest in and accrued and unpaid interest (including all interest accruing subsequent to the commencement of any bankruptcy or similar proceeding, whether or not a claim for post-petition interest is allowable as a claim in any such proceeding), and rent payable on or in connection with, and all fees, costs, expenses and other amounts accrued or due on in connection with Indebtedness, whether outstanding on the Closing Date or thereafter Incurred (including all deferrals, renewals, extensions or refundings of, or amendments, modifications or supplements to, the foregoing), unless in the case of any particular Indebtedness the instrument creating or evidencing the same or the assumption or Guarantee thereof expressly provides that such Indebtedness shall not be senior in right of payment to the Notes or expressly provides that such Indebtedness is *pari passu* or junior to the Notes. Notwithstanding the foregoing, the term Senior Indebtedness shall not include the Company’s 5^{1/2}% Convertible Subordinated Notes due 2009, or Indebtedness of the Company to any Subsidiary of the Company.

“Significant Subsidiary” means any Subsidiary that would be a “Significant Subsidiary” of the Company within the meaning of Rule 1-02(w) under Regulation S-X promulgated by the SEC.

“Spin-Off” has the meaning specified in Section 10.05(d).

“Spin-off Valuation Period” has the meaning specified in Section 10.05(d).

“Stock Price” has the meaning specified in Section 10.04(b).

“Stated Maturity” means, with respect to any security, the date specified in such security as the fixed date on which the final payment of principal of such security is due and payable, including pursuant to any mandatory redemption provision (but excluding any provision providing for the repurchase of such security at the option of the holder thereof upon the happening of any contingency beyond the control of the issuer unless such contingency has occurred).

“Subsidiary” of any Person means any corporation, association, partnership or other business entity of which more than 50% of the total voting power of shares of Capital Stock or other interests (including partnership interests) entitled (without regard to the occurrence of any contingency) to vote in the election of directors, managers or trustees thereof is at the time owned or controlled, directly or indirectly, by (i) such Person, (ii) such Person and one or more Subsidiaries of such Person or (iii) one or more Subsidiaries of such Person.

“TIA” or “Trust Indenture Act” means the Trust Indenture Act of 1939 (15 U.S.C. §§ 77aaa-77bbb), as amended, as in effect on the date of this Indenture.

“Trading Day” has the meaning specified in Section 10.05(g)(iv).

“Trading Price” means, with respect to a Note on any date of determination, the average of the secondary market bid quotations per \$1,000 principal amount of Notes obtained by the

Trustee for \$5,000,000 principal amount of Notes at approximately 3:30 p.m., New York City time, on such determination date from two independent nationally recognized securities dealers selected by the Company, which may include one or more of the Initial Purchasers; provided that if two such bids cannot reasonably be obtained by the Trustee, but one such bid can be reasonably obtained by the Trustee, then this one bid shall be used; and provided further that, if the Trustee cannot reasonably obtain at least one bid for \$5,000,000 principal amount of Notes from a nationally recognized securities dealer, or, in the Company's reasonable judgment, the bid quotations are not indicative of the secondary market value of the Notes, then, for the purpose of determining the Trading Price condition only, the Trading Price per \$1,000 principal amount of Notes shall be deemed to be less than 98% of the product of (a) the Conversion Rate on such determination date and (b) the Closing Sale Price of a share of Common Stock on such determination date.

"Trigger Event" has the meaning specified in Section 10.05(d).

"Trust Officer" means any officer within the Corporate Trust Office of the Trustee with direct responsibility for the administration of this Indenture.

"Trustee" means the party named as such in this Indenture until a successor replaces it and, thereafter, means the successor.

"Uniform Commercial Code" means the New York Uniform Commercial Code as in effect from time to time.

"Wholly Owned Significant Subsidiary" means a Wholly Owned Subsidiary that is also a Significant Subsidiary.

"Wholly Owned Subsidiary" means a Subsidiary of the Company, all the Capital Stock of which (other than directors' qualifying shares) is owned by the Company or another Wholly Owned Subsidiary.

SECTION 1.02. Incorporation by Reference of Trust Indenture Act. This Indenture is subject to the mandatory provisions of the TIA, which are incorporated by reference in and made a part of this Indenture. The following TIA terms have the following meanings:

"**Commission**" means the SEC.

"**indenture securities**" means the Notes.

"**indenture security holder**" means a Noteholder.

"**indenture to be qualified**" means this Indenture.

"**indenture trustee**" or "**institutional trustee**" means the Trustee.

"**obligor**" on the indenture securities means the Company and any other obligor on the indenture securities.

All other TIA terms used in this Indenture that are defined by the TIA, defined by TIA reference to another statute or defined by SEC rule have the meanings assigned to them by such definitions.

SECTION 1.03. Rules of Construction. Unless the context otherwise requires:

- (1) a term has the meaning assigned to it;
- (2) an accounting term not otherwise defined has the meaning assigned to it in accordance with GAAP;
- (3) "or" is not exclusive;
- (4) "including" means including without limitation;
- (5) words in the singular include the plural and words in the plural include the singular;
- (6) unsecured Indebtedness shall not be deemed to be subordinate or junior to Secured Indebtedness merely by virtue of its nature as unsecured Indebtedness;
- (7) the principal amount of any noninterest bearing or other discount security at any date shall be the principal amount thereof that would be shown on a balance sheet of the issuer dated such date prepared in accordance with GAAP; and
- (8) the principal amount of any Preferred Stock shall be (i) the maximum liquidation value of such Preferred Stock or (ii) the maximum mandatory redemption or mandatory repurchase price with respect to such Preferred Stock, whichever is greater.

ARTICLE 2

THE NOTES

SECTION 2.01. Designation, Amount and Issuance of Notes. The Notes shall be designated as "2⁵/₈ % Convertible Subordinated Notes due 2027." The Notes initially will not exceed the aggregate principal amount of \$125,000,000 (up to \$162,500,000 if the Initial Purchasers' option to purchase

additional Notes set forth in the Purchase Agreement is exercised) (except to the extent provided otherwise hereunder) (the “Initial Notes”).

The Company may, without consent of the Noteholders, increase the principal amount of the Notes by issuing additional Notes (“Additional Notes”) in the future on the same terms and conditions, except for any differences in the issue price and interest accrued prior to the issue date of the Additional Notes; provided that such differences do not cause the Additional Notes to constitute a different class of securities than the Initial Notes for U.S. federal income tax purposes; provided further, that the Additional Notes have the same CUSIP or ISIN number as the Initial Notes. The Initial Notes and the Additional Notes will rank equally and ratably and would be treated as a single class of securities for all purposes under this Indenture. No

Additional Notes may be issued if any Event of Default has occurred and is continuing with respect to the Notes.

Upon the execution of this Indenture, or from time to time thereafter, Notes may be executed by the Company and delivered to the Trustee for authentication, and the Trustee shall thereupon authenticate and deliver Notes upon a written order of the Company, such order signed by an Officer or by any Assistant Treasurer of the Company or any Assistant Secretary of the Company, without any further action by the Company hereunder.

SECTION 2.02. Form of the Notes. The Notes and the Trustee’s certificate of authentication to be borne by such Notes shall be substantially in the form set forth in Exhibit A hereto. The terms and provisions contained in the form of Notes attached as Exhibit A hereto shall constitute, and are hereby expressly made, a part of this Indenture and, to the extent applicable, the Company and the Trustee, by their execution and delivery of this Indenture, expressly agree to such terms and provisions and to be bound thereby.

Any of the Notes may have such letters, numbers or other marks of identification and such notations, legends, endorsements or changes as the officers executing the same may approve (execution thereof to be conclusive evidence of such approval) and as are not inconsistent with the provisions of this Indenture, or as may be required by the custodian for the Global Notes, the Depository or by the National Association of Securities Dealers, Inc. in order for the Notes to be tradable on The PORTAL Market or as may be required for the Notes to be tradable on any other market developed for trading of securities pursuant to Rule 144A or as may be required to comply with any applicable law or with any rule or regulation made pursuant thereto or with any rule or regulation of any securities exchange or automated quotation system on which the Notes may be listed, or to conform to usage, or to indicate any special limitations or restrictions to which any particular Notes are subject.

So long as the Notes are eligible for book-entry settlement with the Depository, or unless otherwise required by law, or otherwise contemplated by Section 2.08(b), all of the Notes will be represented by one or more Notes in global form registered in the name of the Depository or the nominee of the Depository (“Global Notes”). The transfer and exchange of beneficial interests in any such Global Notes shall be effected through the Depository in accordance with this Indenture and the applicable procedures of the Depository. Except as provided in Section 2.08(b), beneficial owners of a Global Note shall not be entitled to have certificates registered in their names, will not receive or be entitled to receive physical delivery of certificates in definitive form and will not be considered holders of such Global Note.

Any Global Notes shall represent such of the outstanding Notes as shall be specified therein and shall provide that it shall represent the aggregate amount of outstanding Notes from time to time endorsed thereon and that the aggregate amount of outstanding Notes represented thereby may from time to time be increased or reduced to reflect redemptions, repurchases, conversions, transfers or exchanges permitted hereby. Any endorsement of a Global Note to reflect the amount of any increase or decrease in the amount of outstanding Notes represented thereby shall be made by the Trustee or the custodian for the Global Note, at the direction of the Trustee, in such manner and upon instructions given by the holder of such Notes in accordance

with this Indenture. Payment of principal of, interest on and premium, if any, on any Global Notes shall be made to the Depository in immediately available funds.

SECTION 2.03. Date and Denomination of Notes; Payment at Maturity; Payment of Interest. The Notes shall be issuable in fully registered form without interest coupons in denominations of \$1,000 principal amount and integral multiples thereof. Each Note shall be dated the date of its authentication and shall bear interest from the date specified on the face of the form of Notes attached as Exhibit A hereto. Interest on the Notes shall be computed on the basis of a 360-day year comprised of twelve 30-day months.

On the Maturity Date, each holder shall be entitled to receive on such date \$1,000 principal amount per Notes and accrued and unpaid interest to, but not including, the Maturity Date. With respect to Global Notes, principal and interest will be paid to the Depository in immediately available funds. With respect to any certificated Notes, principal and interest will be payable at the Company’s office or agency, which initially will be the office or agency of the Trustee located at Wells Fargo Bank, N.A., Corporate Trust Services, 608 2nd Avenue South, MAC N9303-120, Minneapolis, MN 55479, Attention: Isis Pharmaceuticals Account Manager.

The Person in whose name any Note is registered on the Register at 5:00 p.m., New York City time, on any Record Date with respect to any interest payment date shall be entitled to receive the interest payable on such interest payment date, except that the interest payable upon maturity, redemption or repurchase following a Fundamental Change will be payable to the Person to whom principal is payable upon maturity or pursuant to such redemption or repurchase following a Fundamental Change (unless the redemption date or the Fundamental Change Repurchase Date, as the case may be, is after a Record Date and on or prior to the corresponding interest payment date, in which case the semi-annual payment of interest becoming due on such interest payment date shall be payable to the holder of such Notes registered as such on the applicable Record Date). Notwithstanding the foregoing, any Notes or portion thereof surrendered for conversion during the period from 5:00 p.m., New York City time, on the Record Date for any interest payment date to 5:00 p.m., New York City time, on the Business Day preceding the applicable interest payment date shall be accompanied by payment, in immediately available funds or other funds acceptable to the Company, of an amount equal to the interest otherwise payable on such interest payment date on the principal amount being converted (excluding any Additional Interest); provided that no such payment need be made (1) if a holder converts its Notes in connection with a redemption and the Company has specified a redemption date that is after a Record Date and on or prior to the next interest payment date, (2) if a holder converts its

Notes in connection with a Fundamental Change and the Company has specified a Fundamental Change Repurchase Date that is after a Record Date and on or prior to the next interest payment date or (3) to the extent of any overdue interest (including Additional Interest), if any exists at the time of conversion with respect to such Notes.

The Company shall pay interest (i) on any Global Notes by wire transfer of immediately available funds to the account of the Depository or its nominee, (ii) on any Notes in certificated form having a principal amount of less than \$2,000,000, by check mailed to the address of the Person entitled thereto as it appears in the Register, provided, however, that at maturity interest will be payable at the office of the Company maintained by the Company for such purposes, which shall initially be an office or agency of the Trustee and (iii) on any Notes in certificated

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form having a principal amount of \$2,000,000 or more, by wire transfer in immediately available funds at the election of the Holder of such Notes duly delivered to the Trustee at least five Business Days prior to the relevant interest payment date, provided, however, that at maturity interest will be payable at the office of the Company maintained by the Company for such purposes, which shall initially be an office or agency of the Trustee. If a payment date is not a Business Day, payment shall be made on the next succeeding Business Day, and no additional interest shall accrue thereon.

Any interest on any Notes which is payable, but is not punctually paid or duly provided for, on any February 15 or August 15 shall be subject to Section 2.13.

SECTION 2.04. Execution and Authentication. An Officer shall sign the Notes for the Company by manual or facsimile signature.

If an Officer whose signature is on a Note no longer holds that office at the time the Trustee authenticates the Note, the Note shall be valid nevertheless.

A Note shall not be valid until an authorized signatory of the Trustee manually signs the certificate of authentication on the Note. The signature shall be conclusive evidence that the Note has been authenticated under this Indenture.

The Trustee shall authenticate and make available for delivery Notes as set forth in Exhibit A.

The Trustee may appoint an authenticating agent reasonably acceptable to the Company to authenticate the Notes. Any such appointment shall be evidenced by an instrument signed by a Trust Officer, a copy of which shall be furnished to the Company. Unless limited by the terms of such appointment, an authenticating agent may authenticate Notes whenever the Trustee may do so. Each reference in this Indenture to authentication by the Trustee includes authentication by such agent. An authenticating agent has the same rights as any Registrar, Paying Agent or agent for service of notices and demands.

SECTION 2.05. Registrar and Paying Agent. The Company shall maintain an office or agency where Notes may be presented for registration of transfer or for exchange (the “**Registrar**”) and an office or agency where Notes may be presented for payment (the “**Paying Agent**”). The Corporate Trust Office shall be considered as one such office or agency of the Company for each of the aforesaid purposes. The Registrar shall keep a register of the Notes (the “**Register**”) and of their transfer and exchange. The Company may have one or more co-registrars and one or more additional paying agents. The term “Paying Agent” includes any additional paying agent, and the term “Registrar” includes any co-registrars. The Company initially appoints the Trustee as (i) Registrar and Paying Agent in connection with the Notes, (ii) the custodian with respect to the Global Notes and (iii) conversion agent.

The Company shall enter into an appropriate agency agreement with any Registrar or Paying Agent not a party to this Indenture, which shall incorporate the terms of the TIA. The agreement shall implement the provisions of this Indenture that relate to such agent. The Company shall notify the Trustee of the name and address of any such agent. If the Company fails to maintain a Registrar or Paying Agent, the Trustee shall act as such and shall be entitled to

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appropriate compensation therefor pursuant to Section 7.07. The Company or any of its domestically organized Wholly Owned Subsidiaries may act as Paying Agent or Registrar.

The Company may remove any Registrar or Paying Agent upon written notice to such Registrar or Paying Agent and to the Trustee; provided, however, that no such removal shall become effective until (1) acceptance of an appointment by a successor as evidenced by an appropriate agreement entered into by the Company and such successor Registrar or Paying Agent, as the case may be, and delivered to the Trustee or (2) notification to the Trustee that the Trustee shall serve as Registrar or Paying Agent until the appointment of a successor in accordance with clause (1) above. The Registrar or Paying Agent may resign at any time upon written notice; provided, however, that the Trustee may resign as Paying Agent or Registrar only if the Trustee also resigns as Trustee in accordance with Section 7.08.

SECTION 2.06. Paying Agent to Hold Money in Trust. On or prior to each due date of the Principal and interest on any Note, the Company shall deposit with the Paying Agent (or if the Company or a Subsidiary is acting as Paying Agent, segregate and hold in trust for the benefit of the Persons entitled thereto) a sum sufficient to pay such Principal and interest when so becoming due. The Company shall require each Paying Agent (other than the Trustee) to agree in writing that the Paying Agent shall hold in trust for the benefit of Noteholders or the Trustee all money held by the Paying Agent for the payment of Principal or of interest on the Notes and shall notify the Trustee of any default by the Company in making any such payment. If the Company or a Subsidiary of the Company acts as Paying Agent, it shall segregate the money held by it as Paying Agent and hold it as a separate trust fund. The Company at any time may require a Paying Agent to pay all money held by it to the Trustee and to account for any funds disbursed by the Paying Agent. Upon complying with this Section, the Paying Agent shall have no further liability for the money delivered to the Trustee.

SECTION 2.07. Noteholder Lists. The Trustee shall preserve in as current a form as is reasonably practicable the most recent list available to it of the names and addresses of Noteholders. If the Trustee is not the Registrar, the Company shall furnish, or cause the Registrar to furnish, to the Trustee, in

writing at least five Business Days before each interest payment date and at such other times as the Trustee may request in writing, a list in such form and as of such date as the Trustee may reasonably require of the names and addresses of Noteholders.

SECTION 2.08. Exchange and Registration of Transfer of Notes; Restrictions on Transfer. (a) The Company shall cause to be kept at the Corporate Trust Office the Register in which, subject to such reasonable regulations as it may prescribe, the Company shall provide for the registration of Notes and of transfers of Notes. The Register shall be in written form or in any form capable of being converted into written form within a reasonably prompt period of time.

Upon surrender for registration of transfer of any Notes to the Registrar or any co-registrar, and satisfaction of the requirements for such transfer set forth in this Section 2.08, the Company shall execute, and the Trustee shall authenticate and deliver, in the name of the designated transferee or transferees, one or more new Notes of any authorized denominations

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and of a like aggregate principal amount and bearing such restrictive legends as may be required by this Indenture.

Notes may be exchanged for other Notes of any authorized denominations and of a like aggregate principal amount, upon surrender of the Notes to be exchanged at any such office or agency maintained by the Company pursuant to Section 4.02. Whenever any Notes are so surrendered for exchange, the Company shall execute, and the Trustee shall authenticate and deliver, the Notes that the holder making the exchange is entitled to receive bearing registration numbers not contemporaneously outstanding.

All Notes issued upon any registration of transfer or exchange of Notes shall be the valid obligations of the Company, evidencing the same debt, and entitled to the same benefits under this Indenture, as the Notes surrendered upon such registration of transfer or exchange.

All Notes presented or surrendered for registration of transfer or for exchange, redemption, repurchase or conversion shall (if so required by the Company or the Registrar) be duly endorsed, or be accompanied by a written instrument or instruments of transfer in form satisfactory to the Company, and the Notes shall be duly executed by the holder thereof or his attorney duly authorized in writing.

No service charge shall be made to any holder for any registration of, transfer or exchange of Notes, but the Company or the Trustee may require payment by the holder of a sum sufficient to cover any tax, assessment or other governmental charge that may be imposed in connection with any registration of transfer or exchange of Notes.

Neither the Company nor the Trustee nor any Registrar shall be required to exchange, issue or register a transfer of (a) any Notes for a period of fifteen calendar days next preceding date of mailing of a notice of redemption, (b) any Notes or portions thereof called for redemption pursuant to Section 3.02, except for the unredeemed portion of any Notes being redeemed in part, (c) any Notes or portions thereof surrendered for conversion pursuant to Article 10, (d) any Notes or portions thereof tendered for repurchase (and not withdrawn) pursuant to Section 3.04 or (e) any Notes or portions thereof tendered for repurchase (and not withdrawn) pursuant to Section 3.05.

(b) The following provisions shall apply only to Global Notes:

(i) Each Global Note authenticated under this Indenture shall be registered in the name of the Depository or a nominee thereof and delivered to such Depository or a nominee thereof or custodian for the Global Note therefor, and each such Global Note shall constitute a single Note for all purposes of this Indenture.

(ii) Notwithstanding any other provision in this Indenture, no Global Notes may be exchanged in whole or in part for Notes registered, and no transfer of a Global Note in whole or in part may be registered, in the name of any Person other than the Depository or a nominee thereof unless (A) the Depository (x) has notified the Company that it is unwilling or unable to continue as Depository for such Global Note or (y) has ceased to be a clearing agency registered under the Exchange Act, and a successor depository has not been appointed by the Company within 90 calendar days, or (B) the

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Company, in its sole discretion, notifies the Trustee in writing that it no longer wishes to have all the Notes represented by Global Notes. Any Global Notes exchanged pursuant to this Section 2.08(b)(ii) shall be so exchanged in whole and not in part.

(iii) In addition, certificated Notes will be issued in exchange for beneficial interests in a Global Note upon request by or on behalf of the Depository in accordance with customary procedures following the request of a beneficial owner seeking to enforce its rights under the Notes or this Indenture, including its rights following the occurrence of an Event of Default.

(iv) Notes issued in exchange for a Global Note or any portion thereof pursuant to clause (ii) or (iii) above shall be issued in definitive, fully registered form, without interest coupons, shall have an aggregate principal amount equal to that of such Global Notes or portion thereof to be so exchanged, shall be registered in such names and be in such authorized denominations as the Depository shall designate and shall bear any legends required hereunder. Any Global Notes to be exchanged shall be surrendered by the Depository to the Trustee, as Registrar, provided that pending completion of the exchange of a Global Note, the Trustee acting as custodian for the Global Notes for the Depository or its nominee with respect to such Global Notes, shall reduce the principal amount thereof, by an amount equal to the portion thereof to be so exchanged, by means of an appropriate adjustment made on the records of the Trustee. Upon any such surrender or adjustment, the Trustee shall authenticate and make available for delivery the Notes issuable on such exchange to or upon the written order of the Depository or an authorized representative thereof.

(v) In the event of the occurrence of any of the events specified in clause (ii) above or upon any request described in clause (iii) above, the Company will promptly make available to the Trustee a sufficient supply of certificated Notes in definitive, fully registered form, without interest coupons.

(vi) Neither any members of, or participants in, the Depository (“**Agent Members**”) nor any other Persons on whose behalf Agent Members may act shall have any rights under this Indenture with respect to any Global Notes registered in the name of the Depository or any nominee thereof, and the Depository or such nominee, as the case may be, may be treated by the Company, the Trustee and any agent of the Company or the Trustee as the absolute owner and holder of such Global Notes for all purposes whatsoever. Notwithstanding the foregoing, nothing herein shall prevent the Company, the Trustee or any agent of the Company or the Trustee from giving effect to any written certification, proxy or other authorization furnished by the Depository or such nominee, as the case may be, or impair, as between the Depository, its Agent Members and any other Person on whose behalf an Agent Member may act, the operation of customary practices of such Persons governing the exercise of the rights of a holder of any Notes.

(vii) At such time as all interests in a Global Note have been redeemed, repurchased, converted, cancelled or exchanged for Notes in certificated form, such Global Note shall, upon receipt thereof, be canceled by the Trustee in accordance with standing procedures and instructions existing between the Depository and the custodian

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for the Global Note. At any time prior to such cancellation, if any interest in a Global Note is redeemed, repurchased, converted, cancelled or exchanged for Notes in certificated form, the principal amount of such Global Note shall, in accordance with the standing procedures and instructions existing between the Depository and the custodian for the Global Note, be appropriately reduced, and an endorsement shall be made on such Global Note, by the Trustee or the custodian for the Global Note, at the direction of the Trustee, to reflect such reduction.

(c) Every Note (and all securities issued in exchange therefor or in substitution thereof) that bears or is required under this Section 2.08(c) to bear the legend set forth in this Section 2.08(c) (together with any Common Stock issued upon conversion of the Notes and required to bear the legend set forth in Exhibit B, collectively, the “**Restricted Securities**”) shall be subject to the restrictions on transfer set forth in this Section 2.08(c) (including those set forth in the legend below and the legend set forth in Exhibit B) unless such restrictions on transfer shall be waived by written consent of the Company following receipt of legal advice supporting the permissibility of the waiver of such transfer restrictions, and the holder of each such Restricted Security, by such holder’s acceptance thereof, agrees to be bound by all such restrictions on transfer. As used in this Section 2.08(c), the term “**transfer**” means any sale, pledge, loan, transfer or other disposition whatsoever of any Restricted Security or any interest therein.

Until the expiration of the holding period applicable to sales of Restricted Securities under Rule 144(k) under the Securities Act (or any successor provision), any certificate evidencing a Restricted Security shall bear a legend in substantially the following form (or as set forth in Exhibit B, in the case of Common Stock issued upon conversion of the Notes), unless such Restricted Security has been sold pursuant to a registration statement that has been declared effective under the Securities Act (and which continues to be effective at the time of such transfer) or sold pursuant to Rule 144 under the Securities Act or any similar provision then in force, or unless otherwise agreed by the Company in writing as set forth above, with written notice thereof to the Trustee:

THE SECURITY EVIDENCED BY THIS CERTIFICATE HAS NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE “**SECURITIES ACT OF 1933**”), OR ANY STATE SECURITIES LAWS, AND MAY NOT BE OFFERED OR SOLD EXCEPT AS SET FORTH IN THE FOLLOWING SENTENCE. BY ACQUISITION HEREOF OR OF A BENEFICIAL INTEREST HEREIN, THE HOLDER AGREES (1) THAT IT WILL NOT PRIOR TO THE DATE TWO YEARS AFTER THE LAST DATE OF ORIGINAL ISSUANCE OF THE 2% % CONVERTIBLE SUBORDINATED NOTES DUE 2027 OF ISIS PHARMACEUTICALS, INC. (THE “**COMPANY**”) RESELL OR OTHERWISE TRANSFER THE SECURITY EVIDENCED HEREBY OR THE COMMON STOCK THAT MAY BE ISSUABLE UPON CONVERSION OF SUCH SECURITY EXCEPT (A) TO THE COMPANY OR ANY SUBSIDIARY THEREOF, (B) TO A PERSON IT REASONABLY BELIEVES IS A QUALIFIED INSTITUTIONAL BUYER IN COMPLIANCE WITH RULE 144A UNDER THE SECURITIES ACT OF 1933, (C) PURSUANT TO A REGISTRATION STATEMENT WHICH HAS BEEN DECLARED EFFECTIVE UNDER THE SECURITIES ACT OF 1933 AND WHICH CONTINUES TO BE EFFECTIVE AT THE TIME OF SUCH TRANSFER, OR (D) PURSUANT TO THE EXEMPTION FROM

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REGISTRATION REQUIREMENTS UNDER THE SECURITIES ACT OF 1933 PROVIDED BY RULE 144, IF AVAILABLE, SUBJECT TO THE COMPANY’S AND THE TRUSTEE’S RIGHT PRIOR TO ANY SUCH TRANSFER, TO REQUIRE THE DELIVERY OF AN OPINION OF COUNSEL, CERTIFICATIONS AND/OR OTHER INFORMATION SATISFACTORY TO THE COMPANY AND THE TRUSTEE; AND (2) THAT IT WILL DELIVER TO EACH PERSON TO WHOM THE SECURITY EVIDENCED HEREBY IS TRANSFERRED PURSUANT TO CLAUSE 1(B) ABOVE A NOTICE SUBSTANTIALLY TO THE EFFECT OF THIS LEGEND.

In connection with any transfer of the Notes prior to the date two years after the last date of original issuance of the Notes (other than a transfer pursuant to clause 1(C) above), the holder must complete and deliver the transfer certificate contained in this Indenture to the Trustee (or any successor Trustee, as applicable). If the proposed transfer is pursuant to clause 1(D) above, the holder must, prior to such transfer, furnish to the Trustee (or any successor Trustee, as applicable), such certifications, legal opinions or other information as the Company may reasonably require to confirm that such transfer is being made pursuant to an exemption from, or in a transaction not subject to, the registration requirements of the Securities Act. The legend set forth above will be removed upon the earlier of the transfer of the security evidenced thereby pursuant to clause 1(C) or 1(D) above or the expiration of two years from the last date of original issuance of the security evidenced thereby.

Any Notes that are Restricted Securities and as to which such restrictions on transfer shall have expired in accordance with their terms or as to conditions for removal of the foregoing legend set forth therein have been satisfied may, upon surrender of such Notes for exchange to the Registrar in accordance with the provisions of this Section 2.08, be exchanged for a new Note or Notes, of like tenor and aggregate principal amount, which shall not bear the restrictive legend required by this Section 2.08(c). If such Restricted Security surrendered for exchange is represented by a Global Note bearing the

legend set forth in this Section 2.08(c), the Principal amount of the legended Global Notes shall be reduced by the appropriate principal amount and the principal amount of a Global Note without the legend set forth in this Section 2.08(c) shall be increased by an equal principal amount. If a Global Note without the legend set forth in this Section 2.08(c) is not then outstanding, the Company shall execute and the Trustee shall authenticate and deliver an unlegended Global Note to the Depository.

(d) Any Restricted Securities, prior to the expiration of the holding period applicable to sales thereof under Rule 144(k) under the Securities Act (or any successor provision), purchased or owned by the Company or any Affiliate thereof may not be resold by the Company or such Affiliate unless registered under the Securities Act or resold pursuant to an exemption from the registration requirements of the Securities Act in a transaction which results in such Notes or Common Stock, as the case may be, no longer being “**restricted securities**” (as defined under Rule 144).

(e) The Trustee shall have no responsibility or obligation to any Agent Members or any other Person with respect to the accuracy of the books or records, or the acts or omissions, of the Depository or its nominee or of any participant or member thereof, with respect to any ownership interest in the Notes or with respect to the delivery to any Agent Member or other Person (other than the Depository) of any notice (including any notice of redemption) or

the payment of any amount, under or with respect to such Notes. All notices and communications to be given to the Noteholders and all payments to be made to Noteholders under the Notes shall be given or made only to or upon the order of the registered Noteholders (which shall be the Depository or its nominee in the case of a Global Note). The rights of beneficial owners in any Global Notes shall be exercised only through the Depository subject to the customary procedures of the Depository. The Trustee may rely and shall be fully protected in relying upon information furnished by the Depository with respect to its Agent Members.

The Trustee shall have no obligation or duty to monitor, determine or inquire as to compliance with any restrictions on transfer imposed under this Indenture or under applicable law with respect to any transfer of any interest in any Notes (including any transfers between or among Agent Members) other than to require delivery of such certificates and other documentation or evidence as are expressly required by, and to do so if and when expressly required by, the terms of this Indenture, and to examine the same to determine substantial compliance as to form with the express requirements hereof.

SECTION 2.09. Replacement Notes. If a mutilated Note is surrendered to the Registrar or if the Noteholder of a Note claims that the Note has been lost, destroyed or wrongfully taken, the Company shall issue and the Trustee shall authenticate a replacement Note if the requirements of Section 8-405 of the Uniform Commercial Code are met, such that the Noteholder (i) satisfies the Company or the Trustee within a reasonable time after he has notice of such loss, destruction or wrongful taking and the Registrar does not register a transfer prior to receiving such notification, (ii) makes such request to the Company or the Trustee prior to the Note being acquired by a protected purchaser as defined in Section 8-303 of the Uniform Commercial Code (a “**protected purchaser**”) and (iii) satisfies any other reasonable requirements of the Trustee. If required by the Trustee or the Company, such Noteholder shall furnish an indemnity bond sufficient in the judgment of the Trustee to protect the Company, the Trustee, the Paying Agent and the Registrar from any loss that any of them may suffer if a Note is replaced. The Company and the Trustee may charge the Noteholder for their expenses in replacing a Note. In case any Note which has matured or is about to mature or has been called for redemption or has been properly tendered for repurchase on a Fundamental Change Repurchase Date (and not withdrawn) or has been tendered for repurchase on a Repurchase Date (and not withdrawn), as the case may be, or is to be converted into Common Stock, shall become mutilated or be destroyed, lost or stolen, the Company may, instead of issuing a substitute Note, pay or authorize the payment of or convert or authorize the conversion of the same (without surrender thereof except in the case of a mutilated Note), as the case may be, if the applicant for such payment or conversion shall furnish to the Company, to the Trustee and, if applicable, to such authenticating agent such security or indemnity as may be required by them to save each of them harmless for any loss, liability, cost or expense caused by or in connection with such substitution, and, in every case of destruction, loss or theft, the applicant shall also furnish to the Company, the Trustee and, if applicable, any Paying Agent or conversion agent evidence to their satisfaction of the destruction, loss or theft of such Note and of the ownership thereof.

Every replacement Note is an additional obligation of the Company.

The provisions of this Section 2.09 are exclusive and shall preclude (to the extent lawful) all other rights and remedies with respect to the replacement or payment of mutilated, lost, destroyed or wrongfully taken Notes.

SECTION 2.10. Outstanding Notes. Notes outstanding at any time are all Notes authenticated by the Trustee except for those canceled by it, those delivered to it for cancellation and those described in this Section as not outstanding. A Note does not cease to be outstanding because the Company or an Affiliate of the Company holds the Note.

If a Note is replaced pursuant to Section 2.09, it ceases to be outstanding unless the Trustee and the Company receive proof satisfactory to them that the replaced Note is held by a protected purchaser.

If the Paying Agent segregates and holds in trust, in accordance with this Indenture, on a redemption date, Repurchase Date or Maturity Date money sufficient to pay all principal and interest payable on that date with respect to the Notes (or portions thereof) to be redeemed, repurchased or maturing, as the case may be, and the Paying Agent is not prohibited from paying such money to the Noteholders on that date pursuant to the terms of this Indenture, then on and after that date such Notes (or portions thereof) cease to be outstanding and interest on them ceases to accrue.

SECTION 2.11. Temporary Notes. Pending the preparation of Notes in certificated form, the Company may execute and the Trustee or an authenticating agent appointed by the Trustee shall, upon the written request of the Company, authenticate and deliver temporary Notes (printed or lithographed). Temporary Notes shall be issuable in any authorized denomination, and substantially in the form of the Notes in certificated form, but with such omissions, insertions and variations as may be appropriate for temporary Notes, all as may be determined by the Company. Every such temporary Note shall be executed by the Company and authenticated by the Trustee or such authenticating agent upon the same conditions and in substantially the same

manner, and with the same effect, as the Notes in certificated form. Without unreasonable delay, the Company will execute and deliver to the Trustee or such authenticating agent Notes in certificated form and thereupon any or all temporary Notes may be surrendered in exchange therefor, at each office or agency maintained by the Company pursuant to Section 4.02 and the Trustee or such authenticating agent shall authenticate and make available for delivery in exchange for such temporary Notes an equal aggregate principal amount of Notes in certificated form. Such exchange shall be made by the Company at its own expense and without any charge therefor. Until so exchanged, the temporary Notes shall in all respects be entitled to the same benefits and subject to the same limitations under this Indenture as Notes in certificated form authenticated and delivered hereunder.

SECTION 2.12. Cancellation. The Company at any time may deliver Notes to the Trustee for cancellation. The Registrar and the Paying Agent shall forward to the Trustee any Notes surrendered to them for registration of transfer, exchange or payment. The Trustee and no one else shall cancel all Notes surrendered for registration of transfer, exchange, payment or cancellation and dispose of such canceled Notes in accordance with its customary procedures or deliver canceled Notes to the Company. The Company may not issue new Notes to replace

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Notes it has redeemed, paid or delivered to the Trustee for cancellation. The Trustee shall not authenticate Notes in place of canceled Notes other than pursuant to the terms of this Indenture.

SECTION 2.13. Defaulted Interest. If the Company defaults in a payment of interest on the Notes, the Company shall pay the defaulted interest (plus interest on such defaulted interest at the rate of 1% per annum above the then applicable interest rate to the extent lawful) in any lawful manner. The Company may pay the defaulted interest to the Persons who are Noteholders on a subsequent special record date. The Company shall fix or cause to be fixed any such special record date and payment date to the reasonable satisfaction of the Trustee and shall promptly deliver or cause to be delivered to each Noteholder a notice that states the special record date, the payment date and the amount of defaulted interest to be paid.

SECTION 2.14. CUSIP and ISIN Numbers. The Company in issuing the Notes may use “CUSIP” and “ISIN” numbers (if then generally in use) and, if so, the Trustee shall use “CUSIP” and “ISIN” numbers in notices of redemption as a convenience to Noteholders; provided, however, that any such notice may state that no representation is made as to the correctness of such numbers either as printed on the Notes or as contained in any notice of a redemption and that reliance may be placed only on the other identification numbers printed on the Notes, and any such redemption shall not be affected by any defect in or omission of such numbers. The Company shall promptly notify the Trustee in writing of any changes to the CUSIP and ISIN numbers.

ARTICLE 3

REDEMPTION AND REPURCHASE OF NOTES

SECTION 3.01. Optional Redemption of Notes. At any time on or after February 15, 2012, the Notes may be redeemed at the option of the Company, in whole or in part, upon notice as set forth in Section 3.02, in cash at the redemption price below. The redemption price for the Notes, expressed as a percentage of principal amount, is as follows for the periods set forth below:

<u>Period</u>	<u>Redemption Price</u>
February 15, 2012 to February 14, 2013	100.750%
February 15, 2013 to February 14, 2014	100.375%
February 15, 2014 and thereafter	100.000%

In addition, the Company will pay interest on the Notes being redeemed, which interest will include such interest accrued and unpaid to, but excluding, the redemption date; provided, that if the redemption date is after a Record Date and on or prior to the corresponding interest payment date, the interest will be paid on the redemption date to the holder of record on the Record Date. The Company may not redeem any Notes if a Default in the payment of interest on the Notes has occurred and is continuing.

SECTION 3.02. Notice of Optional Redemption; Selection of Notes to Be Redeemed. In case the Company shall desire to exercise the right to redeem all or, as the case may be, any part

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of the Notes pursuant to Section 3.01, it shall fix a date for redemption and it or, at its written request received by the Trustee not fewer than five Business Days prior (or such shorter period of time as may be acceptable to the Trustee) to the date the notice of redemption is to be delivered, the Trustee in the name of and at the expense of the Company, shall deliver or cause to be delivered a notice of such redemption not fewer than 30 calendar days nor more than 60 calendar days prior to the redemption date to each record holder of Notes so to be redeemed in whole or in part at its last address as the same appears on the Register; provided that if the Company makes such request of the Trustee, it shall, together with such request, also give written notice of the redemption date to the Trustee, provided that the text of the notice shall be prepared by the Company. The notice, if delivered in the manner herein provided, shall be conclusively presumed to have been duly given, whether or not the holder receives such notice. In any case, failure to deliver such notice or any defect in the notice to the holder of any Notes designated for redemption as a whole or in part shall not affect the validity of the proceedings for the redemption of any other Notes. Concurrently with the delivery of any such notice of redemption, the Company shall issue a press release announcing such redemption, the form and content of which press release shall be determined by the Company in its sole discretion. The failure to issue any such press release or any defect therein shall not affect the validity of the redemption notice or any of the proceedings for the redemption of any Notes called for redemption.

Each such notice of redemption shall specify: (i) the aggregate principal amount of Notes to be redeemed, (ii) the CUSIP number or numbers of the Notes being redeemed, (iii) the date fixed for redemption (which shall be a Business Day), (iv) the redemption price at which Notes are to be redeemed, (v) the place or places of payment and that payment will be made upon presentation and surrender of such Notes, (iv) that interest accrued and unpaid to, but excluding, the date fixed for redemption will be paid as specified in said notice, and that on and after said date interest thereon or on the portion thereof to be redeemed will cease to accrue, (vii) that the holder has a right to convert the Notes called for redemption, (viii) the Conversion Rate on the date of such

notice, (ix) the time and date on which the right to convert such Notes or portions thereof will expire, (x) the formula for determining the amount of cash and the number of shares, if any, to be delivered to the holder upon conversion pursuant to Section 10.12 and the date on which the Cash Settlement Averaging Period begins, (xi) whether the Company has elected to settle its obligation upon conversion by delivering shares of Common Stock, cash or a combination of cash and shares of Common Stock, and, in the event that the Company has elected to deliver all or a portion of its conversion obligation in cash, the date on which the Conversion Period will begin and (xii) that the Company will pay cash for fractional interests in shares of Common Stock, if any, as provided in this Indenture. If fewer than all the Notes are to be redeemed, the notice of redemption shall identify the Notes to be redeemed (including CUSIP numbers, if any). In case any Notes are to be redeemed in part only, the notice of redemption shall state the portion of the principal amount thereof to be redeemed and shall state that, on and after the redemption date, upon surrender of such Notes, a new Notes or Notes in principal amount equal to the unredeemed portion thereof will be issued.

Whenever any Notes are to be redeemed, the Company will give the Trustee written notice of the redemption date, together with an Officer's Certificate as to the aggregate principal amount of Notes to be redeemed not fewer than 35 calendar days (or such shorter period of time as may be acceptable to the Trustee) prior to the redemption date.

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On or prior to the redemption date specified in the notice of redemption given as provided in this Section 3.02, the Company will deposit with the Paying Agent (or, if the Company is acting as its own Paying Agent, set aside, segregate and hold in trust as provided in Section 2.06) an amount of money in immediately available funds sufficient to redeem on the redemption date all the Notes (or portions thereof) so called for redemption (other than those theretofore surrendered for conversion into Common Stock) at the appropriate redemption price, together with accrued and unpaid interest to, but excluding, the redemption date; provided that if such payment is made on the redemption date, it must be received by the Paying Agent, by 11:00 a.m., New York City time, on such date. If any Notes called for redemption are converted pursuant hereto prior to such redemption date, any money deposited with the Paying Agent or so segregated and held in trust for the redemption of such Notes shall be paid to the Company or, if then held by the Company, shall be discharged from such trust.

If less than all of the outstanding Notes are to be redeemed, the Trustee shall select the Notes or portions thereof of the Global Notes or the Notes in certificated form to be redeemed (in principal amounts of \$1,000 or multiples thereof) by lot, on a pro rata basis or by another method the Trustee deems fair and appropriate. If any Notes selected for redemption are submitted for conversion in part after such selection, the portion of such Notes submitted for conversion shall be deemed (so far as may be possible) to be the portion to be selected for redemption. The Notes (or portions thereof) so selected for redemption shall be deemed duly selected for redemption for all purposes hereof, notwithstanding that any such Notes are submitted for conversion in part before the delivery of the notice of redemption.

Upon any redemption of less than all of the outstanding Notes, the Company and the Trustee may (but need not), solely for purposes of determining the pro rata allocation among such Notes that are unconverted and outstanding at the time of redemption, treat as outstanding any Notes surrendered for conversion during the period of fifteen calendar days preceding the delivery of a notice of redemption and may (but need not) treat as outstanding any Notes authenticated and delivered during such period in exchange for the unconverted portion of any Notes converted in part during such period.

SECTION 3.03. Payment of Notes Called for Redemption. If notice of redemption has been given as provided in Section 3.02, the Notes or portion of Notes with respect to which such notice has been given shall, unless converted pursuant to the terms hereof, become due and payable on the date fixed for redemption and at the place or places stated in such notice at the redemption price set forth in the notice of redemption, plus interest accrued and unpaid to, but excluding, the redemption date (unless the redemption date is after a Record Date and on or prior to the corresponding interest payment date, in which event the interest will be paid on the interest payment date to the holder of record on the Record Date), and, unless the Company shall default in the payment of such Notes at the redemption price, plus interest, if any, accrued and unpaid to, but excluding, such date, interest on the Notes or portion of Notes so called for redemption, interest shall cease to accrue on and after such date and, after 5:00 p.m., New York City time, on the Business Day immediately preceding the redemption date (unless the Company shall default in the payment of such Notes at the redemption price, together with interest accrued to such date) such Notes shall cease to be convertible pursuant to Article 10 and, except as provided in Section 2.06 and Section 8.02, to be entitled to any benefit or security under this Indenture, and the holders thereof shall have no right in respect of such Notes except the right to receive the

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redemption price thereof plus accrued and unpaid interest to, but excluding, the redemption date. On presentation and surrender of such Notes at a place of payment in said notice specified, the said Notes or the specified portions thereof shall be paid and redeemed by the Company at the redemption price, together with interest accrued and unpaid thereon to, but excluding, the redemption date; provided that if the applicable redemption date is after the applicable Record Date and on or before an interest payment date, the interest payable on such interest payment date shall be paid on such interest payment date to the holders of record of such Notes on the applicable Record Date instead of the holders surrendering such Notes for redemption on such date.

Upon presentation of any Notes redeemed in part only, the Company shall execute and the Trustee shall authenticate and make available for delivery to the holder thereof, at the expense of the Company, a new Notes or Notes, of authorized denominations, in principal amount equal to the unredeemed portion of the Notes so presented.

Notwithstanding the foregoing, the Trustee shall not redeem any Notes or deliver any notice of redemption during the occurrence or continuance of a Default in payment of interest on the Notes. If any Notes called for redemption shall not be so paid upon surrender thereof for redemption on the redemption date as provided in this Section 3.03, such Notes shall remain convertible into Common Stock until the redemption price and interest shall have been paid or duly provided for.

SECTION 3.04. Repurchase at Option of Holders Upon a Fundamental Change. (a) If there shall occur a Fundamental Change at any time prior to maturity of the Notes, then each holder of Notes shall have the right, at such holder's option, to require the Company to repurchase all of such holder's Notes, or any portion thereof that is a multiple of \$1,000 principal amount, on a date (the "**Fundamental Change Repurchase Date**") specified by the Company, that is not less than 15 calendar days nor more than 35 calendar days after the date of the Company Repurchase Notice related to such Fundamental Change at

a cash repurchase price equal to 100% of the Principal amount of the Notes being repurchased, plus accrued and unpaid interest to, but excluding, the Fundamental Change Repurchase Date, subject to the satisfaction by the holder of the requirements set forth in Section 3.04(c); provided that if such Fundamental Change Repurchase Date falls after a Record Date and on or prior to the corresponding interest payment date, then the interest payable on such interest payment date shall be paid on such interest payment date to the holders of record of the Notes on the applicable Record Date instead of the holders surrendering the Notes for repurchase on such date.

(b) Within 20 calendar days after the occurrence of a Fundamental Change, the Company shall deliver or cause to be delivered to all holders of record of the Notes on the date of the Fundamental Change at their addresses shown in the Register (and to beneficial owners of the Notes as required by applicable law) a Company Repurchase Notice as set forth in Section 3.06 with respect to such Fundamental Change. The Company shall also deliver a copy of the Company Repurchase Notice to the Trustee and the Paying Agent at such time as it is delivered to Noteholders. Concurrently with the delivery of such Company Repurchase Notice, the Company shall issue a press release announcing such Fundamental Change referred to in the Company Repurchase Notice, the form and content of which press release shall be determined by the Company in its sole discretion.

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No failure of the Company to give the foregoing notices and press release and no defect therein shall limit the repurchase rights of Noteholders or affect the validity of the proceedings for the repurchase of the Notes pursuant to this Section 3.04.

(c) For Notes to be repurchased at the option of the holder, the holder must deliver to the Paying Agent, prior to 5:00 p.m., New York City time, on the Business Day immediately preceding the Fundamental Change Repurchase Date, (i) a written notice of repurchase (the “**Repurchase Notice**”) in the form set forth on the reverse of the Notes duly completed (if the Notes are certificated) or stating the following (if the Notes are represented by a Global Note): (A) the certificate number of the Notes which the holder will deliver to be repurchased or compliance with the appropriate Depository procedures, (B) the portion of the Principal amount of the Notes which the holder will deliver to be repurchased, which portion must be in principal amounts of \$1,000 or an integral multiple of \$1,000 and (C) that such Notes shall be repurchased by the Company pursuant to the terms and conditions specified in the Notes and in this Indenture, together with (ii) such Notes duly endorsed for transfer (if the Notes are certificated) or book-entry transfer of such Notes (if such Notes are represented by a Global Note). The delivery of such Notes to the Paying Agent with, or at any time after delivery of, the Repurchase Notice (together with all necessary endorsements) at the office of the Paying Agent shall be a condition to the receipt by the holder of the repurchase price therefore; provided, however, that such repurchase price shall be so paid pursuant to this Section 3.04 only if the Notes so delivered to the Paying Agent shall conform in all respects to the description thereof in the Repurchase Notice. All questions as to the validity, eligibility (including time of receipt) and acceptance of any Notes for repurchase shall be determined by the Company, whose determination shall be final and binding absent manifest error.

(d) The Company shall repurchase from the holder thereof, pursuant to this Section 3.04, a portion of a Note, if the principal amount of such portion is \$1,000 or a whole multiple of \$1,000. Provisions of this Indenture that apply to the repurchase of all of a Note also apply to the repurchase of such portion of such Note.

(e) The Paying Agent shall promptly notify the Company of the receipt by it of any Repurchase Notice or written notice of withdrawal thereof.

Any repurchase by the Company contemplated pursuant to the provisions of this Section 3.04 shall be consummated by the delivery of the consideration to be received by the holder promptly following the later of the Fundamental Change Repurchase Date and the time of the book-entry transfer or delivery of the Notes.

SECTION 3.05. Repurchase of Notes by the Company at the Option of Holders. (a) Each holder of Notes shall have the right, at such holder’s option, to require the Company to repurchase all of such holder’s Notes, or any portion thereof that is a multiple of \$1,000 principal amount, on February 15, 2014, February 15, 2017 and February 15, 2022 (each, a “**Repurchase Date**”), at a repurchase price of 100% of the Principal amount of the Notes being repurchased, plus accrued and unpaid interest to, but excluding, the Repurchase Date, provided that if such Repurchase Date falls after a Record Date and on or prior to the corresponding interest payment date, then the interest payable on such interest

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payment date shall be paid on such interest payment date to the holders of record of the Notes on the applicable Record Date instead of the holders surrendering the Notes for repurchase on such date.

(b) On or before the twentieth Business Day prior to each Repurchase Date, the Company shall deliver or cause to be delivered to all holders of record on such date (and to beneficial owners as required by applicable law) at their addresses shown in the Register a Company Repurchase Notice as set forth in Section 3.06. The Company shall also deliver a copy of the Company Repurchase Notice to the Trustee and the Paying Agent at such time as it is delivered to Noteholders.

No failure of the Company to give the foregoing notices and no defect therein shall limit the repurchase rights of Noteholders or affect the validity of the proceedings for the repurchase of the Notes pursuant to this Section 3.05.

(c) For Notes to be so repurchased at the option of the holder, the holder must deliver to the Paying Agent, at any time during the period beginning at 9:00 a.m., New York City time, on the date that is 20 Business Days prior to the applicable Repurchase Date and ending at 5:00 p.m., New York City time, on the Business Day immediately preceding the applicable Repurchase Date, (i) a Repurchase Notice in the form set forth on the reverse of the Notes duly completed (if the Notes are certificated) or stating the following (if the Notes are represented by a Global Note): (A) the certificate number of the Notes which the holder will deliver to be repurchased or compliance with the appropriate Depository procedures, (B) the portion of the Principal amount of the Notes which the holder will deliver to be repurchased, which portion must be in principal amounts of \$1,000 or an integral multiple of \$1,000, and (C) that such Notes shall be repurchased by the Company pursuant to the terms and conditions specified in the Notes and in this Indenture, together with (ii) such Notes duly endorsed for transfer (if the Notes are certificated) or book-entry transfer of such Notes (if such Notes are represented by a Global Note).

The delivery of such Notes to the Paying Agent with, or at any time after delivery of, the Repurchase Notice (together with all necessary endorsements) at the office of the Paying Agent shall be a condition to the receipt by the holder of the repurchase price therefore; provided, however, that such repurchase price shall be so paid pursuant to this Section 3.05 only if the Notes so delivered to the Paying Agent shall conform in all respects to the description thereof in the Repurchase Notice. All questions as to the validity, eligibility (including time of receipt) and acceptance of any Notes for repurchase shall be determined by the Company, whose determination shall be final and binding absent manifest error.

(d) The Company shall repurchase from the holder thereof, pursuant to this Section 3.05, a portion of a Note, if the principal amount of such portion is \$1,000 or a whole multiple of \$1,000. Provisions of this Indenture that apply to the repurchase of all of a Note also apply to the repurchase of such portion of such Notes.

(e) The Paying Agent shall promptly notify the Company of the receipt by it of any Repurchase Notice or written notice of withdrawal thereof.

Any repurchase by the Company contemplated pursuant to the provisions of this Section 3.05 shall be consummated by the delivery of the consideration to be received by the holder

promptly following the later of the Repurchase Date and the time of the book-entry transfer or delivery of the Notes.

SECTION 3.06. Company Repurchase Notice. In connection with any repurchase of Notes, the Company shall, in the case of a Fundamental Change, within 20 calendar days after the occurrence of such Fundamental Change or, no less than 20 Business Days prior to each Repurchase Date, give notice to holders (with a copy to the Trustee) setting forth information specified in this Section 3.06 (in either case, the “**Company Repurchase Notice**”).

Each Company Repurchase Notice shall:

- (1) state the repurchase price and the Fundamental Change Repurchase Date or the Repurchase Date to which the Company Repurchase Notice relates;
- (2) state, if applicable, the circumstances constituting the Fundamental Change;
- (3) state that the repurchase price will be paid in cash;
- (4) state that holders must exercise their right to elect repurchase prior to 5:00 p.m., New York City time, on the Business Day immediately preceding the Fundamental Change Repurchase Date or Repurchase Date, as the case may be;
- (5) include a form of Repurchase Notice;
- (6) state the name and address of the Paying Agent;
- (7) state that Notes must be surrendered to the Paying Agent to collect the repurchase price;
- (8) state that a holder may withdraw its Repurchase Notice at any time prior to 5:00 p.m., New York City time, on the Business Day immediately preceding the Fundamental Change Repurchase Date or the Repurchase Date, as the case may be, by delivering a valid written notice of withdrawal in accordance with Section 3.07;
- (9) state whether the Notes are then convertible, the then applicable Conversion Rate, including, in the case of the occurrence of a Fundamental Change, expected changes in the Conversion Rate resulting from such Fundamental Change transaction and expected changes in the cash, shares or other property deliverable upon conversion of the Notes as a result of the occurrence of the Fundamental Change;
- (10) that Notes as to which a Repurchase Notice has been given may be converted only if the Repurchase Notice is withdrawn in accordance with the terms of this Indenture;
- (11) state the amount of interest accrued and unpaid per \$1,000 principal amount of Notes to, but excluding, the Fundamental Change Repurchase Date and Repurchase Date, as the case may be; and

- (12) state the CUSIP number of the Notes.

A Company Repurchase Notice may be given by the Company or, at the Company’s request, the Trustee shall give such Company Repurchase Notice in the Company’s name and at the Company’s expense; provided, that the text of the Company Repurchase Notice shall be prepared by the Company.

The Company will, to the extent applicable, comply with the provisions of Rule 13e-4 (or any successor provision) and any other tender offer rules under the Exchange Act that may be applicable at the time of the repurchase of the Notes, file the related Schedule TO (or any successor schedule, form or report) or any other schedule required under the Exchange Act and comply with all other federal and state securities laws in connection with the repurchase of the Notes.

SECTION 3.07. Effect of Repurchase Notice; Withdrawal. Upon receipt by the Paying Agent of the Repurchase Notice specified in Section 3.04 or Section 3.05, the holder of the Notes in respect of which such Repurchase Notice was given shall (unless such Repurchase Notice is validly withdrawn in accordance with the following paragraph) thereafter be entitled to receive solely the repurchase price with respect to such Notes. Such repurchase price shall be paid to such holder, subject to receipt of funds and/or the Notes by the Paying Agent, promptly following the later of (x) the Fundamental Change Repurchase Date or the Repurchase Date with respect to such Notes (provided the holder has satisfied the conditions in Section 3.04 or Section 3.05) and (y) the time of book-entry transfer or delivery of such Notes to the Paying Agent by the holder thereof in the manner required by Section 3.04 or Section 3.05. The Notes in respect of which a Repurchase Notice has been given by the holder thereof may not be converted pursuant to Article 10 hereof on or after the date of the delivery of such Repurchase Notice unless such Repurchase Notice has first been validly withdrawn.

A Repurchase Notice may be withdrawn by means of a written notice of withdrawal delivered to the office of the Paying Agent in accordance with the Repurchase Notice at any time prior to 5:00 p.m., New York City time, on the Business Day immediately preceding the Fundamental Change Repurchase Date or Repurchase Date, as the case may be, specifying:

- (a) the certificate number, if any, of the Notes in respect of which such notice of withdrawal is being submitted, or the appropriate Depository information, in accordance with appropriate Depository procedures, if the Notes in respect of which such notice of withdrawal is being submitted is represented by a Global Note,
- (b) the Principal amount of the Notes with respect to which such notice of withdrawal is being submitted, and
- (c) the principal amount, if any, of such Notes which remains subject to the original Repurchase Notice and which has been or will be delivered for repurchase by the Company.

If a Repurchase Notice is properly withdrawn, the Company shall not be obligated to repurchase the Notes listed in such Repurchase Notice.

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SECTION 3.08. Deposit of Repurchase Price. Prior to 10:00 a.m., New York City Time, on the Fundamental Change Repurchase Date or the Repurchase Date, the Company shall deposit with the Paying Agent or, if the Company is acting as the Paying Agent, shall segregate and hold in trust as provided in Section 6.04, an amount of cash (in immediately available funds if deposited on the Fundamental Change Repurchase Date or the Repurchase Date, as the case may be), sufficient to pay the aggregate repurchase price of all the Notes or portions thereof that are to be repurchased as of the Fundamental Change Repurchase Date or the Repurchase Date, as the case may be.

If on the Business Day immediately following the Fundamental Change Repurchase Date or the Repurchase Date the Paying Agent holds cash sufficient to pay the repurchase price of the Notes that holders have elected to require the Company to repurchase in accordance with Section 3.04 or 3.05, as the case may be, then, as of the Fundamental Change Repurchase Date or the Repurchase Date, as the case may be, such Notes will cease to be outstanding, interest (including Additional Interest, if any) shall cease to accrue and all other rights of the holders of such Notes will terminate, other than the right to receive the repurchase price upon delivery or book-entry transfer of the Notes. This will be the case whether or not book-entry transfer of the Notes has been made or the Notes have been delivered to the Paying Agent.

SECTION 3.09. Notes Repurchased in Part. Upon presentation of any Notes repurchased only in part, the Company shall execute and the Trustee shall authenticate and make available for delivery to the holder thereof, at the expense of the Company, a new Note or Notes, of any authorized denomination, in aggregate principal amount equal to the unreurchased portion of the Notes presented.

ARTICLE 4

COVENANTS

SECTION 4.01. Payment of Notes. The Company shall promptly pay the principal of and interest on the Notes on the dates and in the manner provided in the Notes and in this Indenture. Principal and interest shall be considered paid on the date due if on such date the Trustee or the Paying Agent holds in accordance with this Indenture money sufficient to pay all principal and interest then due and the Trustee or the Paying Agent, as the case may be, is not prohibited from paying such money to the Noteholders on that date pursuant to the terms of this Indenture.

The Company shall pay interest on overdue principal at the rate specified therefor in the Notes, and it shall pay interest on overdue installments of interest at the same rate to the extent lawful.

SECTION 4.02. Maintenance of Office or Agency. The Company will maintain an office or agency, where the Notes may be surrendered for registration of transfer or exchange or for presentation for payment or for conversion, redemption or repurchase and where notices and demands to or upon the Company in respect of the Notes and this Indenture may be served. As of the date of this Indenture, such office is located at the office of the Trustee located at Wells Fargo Bank, N.A., Corporate Trust Services, 608 2nd Avenue South, MAC N9303-120,

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Minneapolis, MN 55479, Attention: Isis Pharmaceuticals Account Manager and, at any other time, at such other address as the Trustee may designate from time to time by notice to the Company. The Company will give prompt written notice to the Trustee of the location, and any change in the location, of such office or agency not designated or appointed by the Trustee. If at any time the Company shall fail to maintain any such required office or agency or shall fail to furnish the Trustee with the address thereof, such presentations, surrenders, notices and demands may be made or served at the Corporate Trust Office.

The Company may also from time to time designate co-registrars and one or more offices or agencies where the Notes may be presented or surrendered for any or all such purposes and may from time to time rescind such designations. The Company will give prompt written notice to the Trustee of

any such designation or rescission and of any change in the location of any such other office or agency.

So long as the Trustee is the Registrar, the Trustee agrees to deliver, or cause to be delivered, the notices set forth in Section 7.08. If co-registrars have been appointed in accordance with this Section, the Trustee shall mail such notices only to the Company and the Noteholders it can identify from its records.

SECTION 4.03. Reports; 144A Information. The Company shall deliver (which delivery may be via electronic mail) to the Trustee within 15 days after it files them with the SEC copies of the annual reports and of the information, documents and other reports (or copies of such portions of any of the foregoing as the SEC may by rules and regulations prescribe) which the Company is required to file with the SEC pursuant to Section 13 or 15(d) of the Exchange Act; provided, however, the Company shall not be required to deliver to the Trustee any materials for which the Company has sought and received confidential treatment by the SEC. The Company covenants and agrees that it shall, during any period in which it is not subject to Section 13 or 15(d) under the Exchange Act, make available to any holder or beneficial holder of Notes or any Common Stock issued upon conversion thereof which continue to be Restricted Securities and any prospective purchaser of Notes or such Common Stock designated by such holder or beneficial holder, the information required pursuant to Rule 144A(d)(4) under the Securities Act upon the request of any holder or beneficial holder of the Notes or such Common Stock, all to the extent required to enable such holder or beneficial holder to sell its Notes or Common Stock without registration under the Securities Act within the limitation of the exemption provided by Rule 144A. The Company also shall comply with the provisions of Section 314(a) of the TIA.

SECTION 4.04. Existence. Subject to Article 5, the Company will do or cause to be done all things necessary to preserve and keep in full force and effect its existence and rights (charter and statutory); provided that the Company shall not be required to preserve any such right if the Company shall determine that the preservation thereof is no longer desirable in the conduct of the business of the Company and that the loss thereof is not disadvantageous in any material respect to the Noteholders.

SECTION 4.05. Payment of Taxes and Other Claims. The Company will pay or discharge, or cause to be paid or discharged, before the same may become delinquent, (i) all taxes, assessments and governmental charges levied or imposed upon the Company or upon the

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income, profits or property of the Company, (ii) all claims for labor, materials and supplies which, if unpaid, might by law become a lien or charge upon the property of the Company and (iii) all stamp taxes and other duties, if any, which may be imposed by the United States or any political subdivision thereof or therein in connection with the issuance, transfer, exchange, conversion, redemption or repurchase of any Notes or with respect to this Indenture; provided that, in the case of clauses (i) and (ii), the Company shall not be required to pay or discharge or cause to be paid or discharged any such tax, assessment, charge or claim (A) if the failure to do so will not, in the aggregate, have a material adverse impact on the Company, or (B) if the amount, applicability or validity is being contested in good faith by appropriate proceedings.

SECTION 4.06. Compliance Certificate. The Company shall deliver to the Trustee within 120 days after the end of each fiscal year of the Company an Officer's Certificate stating that a review of the Company's activities during the preceding fiscal year has been made under the supervision of the signing Officer with a view to determining whether the Company has kept, observed, performed and fulfilled its obligations under this Indenture and further stating, as to such Officer signing such certificate, whether to the best of such Officer's knowledge the Company during such preceding fiscal year has kept, observed, performed and fulfilled each and every such covenant contained in this Indenture and that in the course of the performance by the signer of his or her duties as an Officer of the Company such Officer would normally have knowledge of any Default and whether or not the signer knows of any Default that occurred during such period. If such Officer does know of any Default, the certificate shall describe the Default, its status and what action the Company is taking or proposes to take with respect thereto.

SECTION 4.07. Further Instruments and Acts. The Company shall execute and deliver such further instruments and do such further acts as may be reasonably necessary or proper to carry out more effectively the purpose of this Indenture.

SECTION 4.08. Additional Interest Notice. In the event that the Company is required to pay Additional Interest to Noteholders pursuant to the Registration Rights Agreement, the Company will provide written notice ("**Additional Interest Notice**") to the Trustee of its obligation to pay Additional Interest no later than fifteen calendar days prior to the proposed payment date for Additional Interest, and the Additional Interest Notice shall set forth the amount of Additional Interest to be paid by the Company on such payment date. The Trustee shall not at any time be under any duty or responsibility to any holder of Notes to determine the Additional Interest, or with respect to the nature, extent or calculation of the amount of Additional Interest when made, or with respect to the method employed in such calculation of the Additional Interest.

ARTICLE 5

SUCCESSOR COMPANY

SECTION 5.01. When Company May Merge or Transfer Assets. The Company shall not, in a single transaction or a series of related transactions, consolidate with or merge with or

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into, or sell, convey, transfer or lease its property and assets substantially as an entirety to any Person unless:

(a) either (i) the Company is the continuing corporation, or (ii) the resulting, surviving or transferee Person (if other than the Company) is a corporation or limited liability company organized and existing under the laws of the United States, any state thereof or the District of Columbia and such Person assumes, by a supplemental indenture in a form reasonably satisfactory to the Trustee, and a supplemental agreement, all of the Company's obligations under the Notes, this Indenture and the Registration Rights Agreement;

- (b) immediately after giving effect to the transaction described above, no Default or Event of Default, has occurred and is continuing;
- (c) if as a result of such transaction the Notes become convertible into common stock or other securities issued by a third party, such third party fully and unconditionally Guarantees all obligations of the Company or such successor Person under the Notes, this Indenture and the Registration Rights Agreement; and
- (d) the Company has delivered to the Trustee the Officer's Certificate, and if requested, the Opinion of Counsel, pursuant to Section 5.03.

SECTION 5.02. Successor to be Substituted. In case of any such consolidation, merger, sale, conveyance, transfer or lease in which the Company is not the continuing corporation upon the assumption by the successor Person, by supplemental indenture, executed and delivered to the Trustee and reasonably satisfactory in form and substance to the Trustee, of the due and punctual payment of the Principal of, and premium, if any, and interest on all of the Notes, and the due and punctual performance and observance of all of the covenants and conditions of this Indenture to be performed or satisfied by the Company, and by supplemental agreement, executed and delivered to the Trustee and reasonably satisfactory in form and substance to the Trustee, of all of the obligations of the Company under the Registration Rights Agreement, such successor Person shall succeed to and be substituted for the Company and may exercise every right and power of the Company, with the same effect as if it had been named herein as the party of this first part, and the Company shall be discharged from its obligations under the Notes, this Indenture and the Registration Rights Agreement. Such successor Person thereupon may cause to be signed, and may issue either in its own name or in the name of the Company any or all of the Notes, issuable hereunder that theretofore shall not have been signed by the Company and delivered to the Trustee; and, upon the order of such successor Person instead of the Company and subject to all the terms, conditions and limitations in this Indenture prescribed, the Trustee shall authenticate and shall deliver, or cause to be authenticated and delivered, any Notes that previously shall have been signed and delivered by the officers of the Company to the Trustee for authentication, and any Notes that such successor Person thereafter shall cause to be signed and delivered to the Trustee for that purpose. All the Notes so issued shall in all respects have the same legal rank and benefit under this Indenture as the Notes theretofore or thereafter issued in accordance with the terms of this Indenture as though all of such Notes had been issued at the date of the execution hereof. In the event of any such consolidation, merger, sale, conveyance, transfer or lease, upon compliance with this Article 5 the Person named as the "Company" in the first paragraph of this Indenture or any successor that shall thereafter have become such in the

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manner prescribed in this Article 5 may be dissolved, wound up and liquidated at any time thereafter and such Person shall be discharged from its liabilities as obligor and maker of the Notes and from its obligations under this Indenture.

SECTION 5.03. Officer's Certificate and Opinion of Counsel to be Given Trustee. Prior to execution of any supplemental indenture pursuant to this Article 5, the Trustee shall receive an Officer's Certificate and, if requested, an Opinion of Counsel, as conclusive evidence that any such consolidation, merger, sale, conveyance, transfer or lease and any such assumption complies with the provisions of this Article 5.

ARTICLE 6

DEFAULTS AND REMEDIES

SECTION 6.01. Events of Default. An "Event of Default" occurs if:

- (a) the Company fails to pay any of interest (including Additional Interest, if any) on the Notes when due and payable and such failure continues for a period of 30 calendar days;
- (b) the Company fails to pay Principal of the Notes when due at its Stated Maturity, or the Company fails to pay the redemption price or repurchase price in respect of any Notes when due, whether or not the payment is prohibited by Article 12 of this Indenture;
- (c) the Company fails to comply with Section 5.01;
- (d) the Company fails to deliver Common Stock (including any Additional Shares), or cash in lieu thereof, or a combination of the foregoing, as required pursuant to Article 10 upon the conversion of any Notes and such failure continues for 15 days following the scheduled settlement date for such conversion;
- (e) the Company fails to provide notice of the anticipated effective date or actual effective date of a Fundamental Change on a timely basis as required in this Indenture;
- (f) the Company fails to comply with any of its agreements contained in the Notes or this Indenture (other than those referred to in (a) through (e) above) and such failure continues for 60 days after the notice specified below;
- (g) the Company or any Wholly Owned Significant Subsidiary pursuant to or within the meaning of any Bankruptcy Law:
 - (1) commences a voluntary case;
 - (2) consents to the entry of an order for relief against it in an involuntary case;
 - (3) consents to the appointment of a Custodian of it or for any substantial part of its property; or

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- (4) makes a general assignment for the benefit of its creditors;
- (5) or takes any comparable action under any foreign laws relating to insolvency;
- (h) a court of competent jurisdiction enters an order or decree under any Bankruptcy Law that:
 - (1) is for relief against the Company or any Wholly Owned Significant Subsidiary in an involuntary case;
 - (2) appoints a Custodian of the Company or any Wholly Owned Significant Subsidiary or for any substantial part of its property; or
 - (3) orders the winding up or liquidation of the Company or any Wholly Owned Significant Subsidiary;
 - (4) or any similar relief is granted under any foreign laws and the order or decree remains unstayed and in effect for 60 days.

The foregoing shall constitute Events of Default whatever the reason for any such Event of Default and whether it is voluntary or involuntary or is effected by operation of law or pursuant to any judgment, decree or order of any court or any order, rule or regulation of any administrative or governmental body.

The term “**Bankruptcy Law**” means Title 11, United States Code, or any similar Federal or state law for the relief of debtors. The term “**Custodian**” means any receiver, trustee, assignee, liquidator, custodian or similar official under any Bankruptcy Law.

A Default under clause (f) above is not an Event of Default until the Trustee or the Noteholders of at least 25% in Principal amount of the outstanding Notes notify the Company of the Default and the Company does not cure such Default within the time specified after receipt of such notice. Such notice must specify the Default, demand that it be remedied and state that such notice is a “**Notice of Default.**”

The Company shall promptly deliver to the Trustee, written notice in the form of an Officer’s Certificate of any event which with the giving of notice or the lapse of time would become an Event of Default, its status and what action the Company is taking or proposes to take with respect thereto.

SECTION 6.02. Acceleration.

(a) If an Event of Default (other than an Event of Default specified in (x) Section 6.01(f) with respect to the Company’s obligations under Section 4.03 as described below and (y) Section 6.01(g) or (h) with respect to the Company) occurs and is continuing, the Trustee by notice to the Company, or the Noteholders of at least 25% in Principal amount of the outstanding Notes by notice to the Company, may declare the Principal of and accrued but unpaid interest on all the Notes to be due and payable. Upon such a declaration, such Principal

and interest shall be due and payable immediately. If an Event of Default specified in Section 6.01(g) or (h) with respect to the Company occurs, the Principal of and accrued and unpaid interest (including Additional Interest, if any) on all the Notes shall *ipso facto* become and be immediately due and payable without any declaration or other act on the part of the Trustee or any Noteholders. The Noteholders of a majority in Principal amount of the Notes by notice to the Trustee may rescind an acceleration and its consequences if the rescission (i) would not conflict with any judgment or decree; (ii) if all existing Events of Default have been cured or waived except nonpayment of Principal or interest that has become due solely because of acceleration; and (iii) if the Company has paid the compensation, expenses, disbursements and advances of the Trustee, its agents and counsel. No such rescission shall affect any subsequent Default or impair any right consequent thereto.

(b) Notwithstanding the foregoing, to the extent elected by the Company, the sole remedy for an Event of Default relating to the failure by the Company to comply with Section 4.03 and for any failure to comply with the requirements of Section 314(a)(1) of the Trust Indenture Act, as applicable, shall for the first 120 days after the occurrence of such an Event of Default consist exclusively of the right to receive special interest on the Notes at an annual rate equal to 0.25% of the Principal amount of the Notes (“**Special Interest**”). The Special Interest shall be paid semi-annually in arrears, with the first semi-annual payment due on the first interest payment date following the date on which the Special Interest began to accrue on any Notes. The Special Interest shall accrue on all outstanding Notes from and including the date on which an Event of Default relating to a failure to comply with Section 4.03 first occurs to but not including the 120th day thereafter (or such earlier date on which the Event of Default shall have been cured or waived). On such 120th day (or earlier, if the Event of Default relating to reporting obligations in Section 4.03 is cured or waived prior to such 120th day), such Special Interest shall cease to accrue and, if the Event of Default relating to reporting obligations in Section 4.03 has not been cured or waived prior to such 120th day, the Notes shall be subject to acceleration as provided in Section 6.02(a) (without giving effect to clause (x) in the parenthetical of the first sentence thereof). The provisions of this Section 6.02(b) shall not affect the rights of Noteholders in the event of the occurrence of any other Event of Default. In the event the Company does not elect to pay Special Interest upon an Event of Default relating to reporting obligations in Section 4.03 in accordance with this paragraph, the Notes shall be subject to acceleration as provided in Section 6.02(a) (without giving effect to clause (x) in the parenthetical of the first sentence thereof). In no event shall the Special Interest, together with any Additional Interest payable pursuant to the Registration Rights Agreement, accrue at an annual rate exceeding 0.50% of the Principal amount of the Notes.

If the Company elects to pay Special Interest as the sole remedy for an Event of Default relating to the failure to comply with Section 4.03 and for any failure to comply with the requirements of Section 314(a)(1) of the Trust Indenture Act, as applicable, in accordance with the immediately preceding paragraph, the Company shall notify all Noteholders and the Trustee and Paying Agent of such election on or before the close of business on the date on which such Event of Default first occurs.

(c) After a declaration of acceleration, but before a judgment or decree for payment of the money due has been obtained by the Trustee, the holders of a majority in

aggregate Principal amount of the Notes outstanding, by written notice to us and the trustee, may rescind and annul such declaration if:

(1) The Company has paid (or deposited with the Trustee a sum sufficient to pay) (1) all overdue interest (including Additional Interest, if any) on all Notes; (2) the principal amount of any Notes that have become due otherwise than by such declaration of acceleration; (3) to the extent that payment of such interest is lawful, interest upon overdue interest (including Additional Interest, if any); and (4) all sums paid or advanced by the Trustee under this indenture and the reasonable compensation, expenses, disbursements and advances of the Trustee, its agents and counsel; and

(2) all Events of Default, other than the non-payment of the principal amount and any accrued and unpaid interest (including Additional Interest, if any) that have become due solely by such declaration of acceleration, have been cured or waived.

SECTION 6.03. Other Remedies. Subject to Section 6.02, if an Event of Default occurs and is continuing, the Trustee may pursue any available remedy to collect the payment of principal of or interest on the Notes or to enforce the performance of any provision of the Notes or this Indenture.

The Trustee may maintain a proceeding even if it does not possess any of the Notes or does not produce any of them in the proceeding. A delay or omission by the Trustee or any Noteholder in exercising any right or remedy accruing upon an Event of Default shall not impair the right or remedy or constitute a waiver of or acquiescence in the Event of Default. No remedy is exclusive of any other remedy. All available remedies are cumulative.

SECTION 6.04. Waiver of Past Defaults. Subject to Section 6.02, the Noteholders of a majority in aggregate Principal amount of the Notes outstanding may, on behalf of all Noteholders by notice to the Trustee may waive an existing Default or Event of Default under this Indenture and its consequences except (i) a Default in the payment of the Principal of or interest (including Additional Interest, if any) on a Note when due, (ii) a Default arising from the failure to redeem or repurchase any Note when required pursuant to the terms of this Indenture, (iii) a Default arising from the failure of the Company to deliver Common Stock (including any Additional Shares), or cash in lieu thereof, or a combination of the foregoing, as applicable upon the conversion of any Notes pursuant to the terms of this Indenture or (iv) a Default in respect of a provision that under Section 9.02 cannot be amended without the consent of each Noteholder affected. When a Default is waived, it is deemed cured, but no such waiver shall extend to any subsequent or other Default or impair any consequent right.

SECTION 6.05. Control by Majority. The Noteholders of a majority in Principal amount of the Notes may direct the time, method and place of conducting any proceeding for any remedy available to the Trustee or of exercising any trust or power conferred on the Trustee. However, the Trustee may refuse to follow any direction that conflicts with law or this Indenture or, subject to Section 7.01, that the Trustee determines is unduly prejudicial to the rights of other Noteholders or would involve the Trustee in personal liability; provided, however, that the Trustee may take any other action deemed proper by the Trustee that is not inconsistent with such direction. Prior to taking any action hereunder, the Trustee shall be entitled to

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indemnification satisfactory to it in its sole discretion against all losses and expenses caused by taking or not taking such action.

SECTION 6.06. Limitation on Suits. Except to enforce the right to receive payment of principal, premium (if any) or interest when due, no Noteholder may pursue any remedy with respect to this Indenture or the Notes unless:

(a) the Noteholder gives to the Trustee written notice stating that an Event of Default is continuing;

(b) the Noteholders of at least 25% in Principal amount of the Notes make a written request to the Trustee to pursue the remedy and offer reasonable security or indemnity against any costs, liability or expense of the Trustee;

(c) the Trustee does not comply with the request within 60 days after receipt of the request and the offer of security or indemnity; and

(d) the Noteholders of a majority in Principal amount of the Notes do not give the Trustee a direction inconsistent with the request during such 60-day period.

A Noteholder may not use this Indenture to prejudice the rights of another Noteholder or to obtain a preference or priority over another Noteholder.

Notwithstanding any other provision of this Indenture and any provision of any Notes, the right of any holder of any Notes to receive payment of the Principal of (including the redemption price or repurchase price upon redemption or repurchase pursuant to Article 3) and premium, if any, and accrued interest on such Notes, on or after the respective due dates expressed in such Notes or in the event of redemption or repurchase, or to institute suit for the enforcement of any such payment on or after such respective dates against the Company shall not be impaired or affected without the consent of such holder.

Anything contained in this Indenture or the Notes to the contrary notwithstanding, the holder of any Notes, without the consent of either the Trustee or the holder of any other Notes, on its own behalf and for its own benefit, may enforce, and may institute and maintain any proceeding suitable to enforce, its rights of conversion as provided herein.

SECTION 6.07. Rights of Noteholders to Receive Payment. Notwithstanding any other provision of this Indenture, the right of any Noteholder to receive payment of Principal of and interest on the Notes held by such Noteholder, on or after the respective due dates expressed in the Notes, or to bring suit for the enforcement of any such payment on or after such respective dates, shall not be impaired or affected without the consent of such Noteholder.

SECTION 6.08. Collection Suit by Trustee. If an Event of Default specified in Section 6.01(a) or (b) occurs and is continuing, the Trustee may recover judgment in its own name and as trustee of an express trust against the Company for the whole amount then due and owing (together with interest on any unpaid interest to the extent lawful) and the amounts provided for in Section 7.07.

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SECTION 6.09. Trustee May File Proofs of Claim. The Trustee may file such proofs of claim and other papers or documents as may be necessary or advisable in order to have the claims of the Trustee and the Noteholders allowed in any judicial proceedings relative to the Company, their creditors or their property and, unless prohibited by law or applicable regulations, may vote on behalf of the Noteholders in any election of a trustee in bankruptcy or other Person performing similar functions, and any Custodian in any such judicial proceeding is hereby authorized by each Noteholder to make payments to the Trustee and, in the event that the Trustee shall consent to the making of such payments directly to the Noteholders, to pay to the Trustee any amount due it for the reasonable compensation, expenses, disbursements and advances of the Trustee, its agents and its counsel, and any other amounts due the Trustee under Section 7.07.

SECTION 6.10. Priorities. Subject to Article 12, if the Trustee collects any money or property pursuant to this Article 6, it shall pay out the money or property in the following order:

FIRST: to the Trustee for amounts due under Section 7.07;

SECOND: to Noteholders for amounts due and unpaid on the Notes for Principal and interest, ratably without preference or priority of any kind, according to the amounts due and payable on the Notes for Principal and interest, respectively; and

THIRD: to the Company.

The Trustee may fix a record date and payment date for any payment to Noteholders pursuant to this Section. At least 15 days before such record date, the Trustee shall deliver to each Noteholder and the Company a notice that states the record date, the payment date and amount to be paid.

SECTION 6.11. Undertaking for Costs. In any suit for the enforcement of any right or remedy under this Indenture or in any suit against the Trustee for any action taken or omitted by it as Trustee, a court in its discretion may require the filing by any party litigant in the suit of an undertaking to pay the costs of the suit, and the court in its discretion may assess reasonable costs, including reasonable attorneys' fees, against any party litigant in the suit, having due regard to the merits and good faith of the claims or defenses made by the party litigant. This Section does not apply to a suit by the Trustee, a suit by a Noteholder pursuant to Section 6.07 or a suit by Noteholders of more than 10% in Principal amount of the Notes or to any suit instituted by any holder of Notes for the enforcement of the payment of the Principal of, or premium, if any, or interest on any Notes on or after the due date expressed in such Notes or to any suit for the enforcement of the right to convert any Notes in accordance with the provisions of Article 10.

SECTION 6.12. Waiver of Stay, Extension or Usury Laws. The Company (to the extent it may lawfully do so) shall not at any time insist upon, or plead, or in any manner whatsoever claim or take the benefit or advantage of, any stay, extension or usury law wherever enacted, now or at any time hereafter in force, which may affect the covenants or the performance of this Indenture; and the Company (to the extent such that it may lawfully do so) hereby expressly waives all benefit or advantage of any such law, and shall not hinder, delay or impede the

execution of any power herein granted to the Trustee, but shall suffer and permit the execution of every such power as though no such law had been enacted.

ARTICLE 7

TRUSTEE

SECTION 7.01. Duties of Trustee. (a) If an Event of Default has occurred and is continuing, the Trustee shall exercise the rights and powers vested in it by this Indenture and use the same degree of care and skill in its exercise as a prudent Person would exercise or use under the circumstances in the conduct of such Person's own affairs.

(b) Except during the continuance of an Event of Default:

(1) the Trustee need only perform such duties as are specifically set forth in this Indenture and no implied covenants or obligations shall be read into this Indenture against the Trustee; and

(2) in the absence of bad faith, gross negligence or willful misconduct on its part, the Trustee may conclusively rely, as to the truth of the statements and the correctness of the opinions expressed therein, upon certificates or opinions furnished to the Trustee and conforming to the requirements of this Indenture. However, the Trustee shall examine the certificates and opinions to determine whether or not they conform to the requirements of this Indenture.

(c) The Trustee may not be relieved from liability for its own negligent action, its own negligent failure to act or its own willful misconduct, except that:

(1) this paragraph does not limit the effect of paragraph (b) of this Section;

(2) the Trustee shall not be liable for any error of judgment made in good faith by a Trust Officer unless it is proved that the Trustee was negligent in ascertaining the pertinent facts; and

(3) the Trustee shall not be liable with respect to any action it takes or omits to take in good faith in accordance with a direction received by it pursuant to Section 6.05.

(d) Every provision of this Indenture that in any way relates to the Trustee is subject to paragraphs (a), (b) and (c) of this Section.

(e) The Trustee shall not be liable for interest on any money received by it except as the Trustee may agree in writing with the Company.

- (f) Money held in trust by the Trustee need not be segregated from other funds except to the extent required by law.

(g) No provision of this Indenture shall require the Trustee to expend or risk its own funds or otherwise incur financial liability in the performance of any of its duties hereunder or in the exercise of any of its rights or powers, if it shall have reasonable grounds to believe that repayment of such funds or adequate indemnity against such risk or liability is not reasonably assured to it.

(h) Every provision of this Indenture relating to the conduct or affecting the liability of or affording protection to the Trustee shall be subject to the provisions of this Section and to the provisions of the TIA.

SECTION 7.02. Rights of Trustee. (a) The Trustee may rely on any document believed by it to be genuine and to have been signed or presented by the proper person. The Trustee need not investigate any fact or matter stated in the document.

(b) Before the Trustee acts or refrains from acting, it may require an Officer's Certificate or if requested, an Opinion of Counsel, or both. The Trustee shall not be liable for any action it takes or omits to take in good faith in reliance on the Officer's Certificate or Opinion of Counsel.

(c) The Trustee may act through agents and shall not be responsible for the misconduct or negligence of any agent appointed with due care.

(d) The Trustee shall not be liable for any action it takes or omits to take in good faith which it believes to be authorized or within its rights or powers.

(e) The Trustee may consult with counsel, and the advice or opinion of counsel with respect to legal matters relating to this Indenture and the Notes shall be full and complete authorization and protection from liability in respect to any action taken, omitted or suffered by it hereunder in good faith and in accordance with the advice or opinion of such counsel.

(f) The Trustee shall not be bound to make any investigation into the facts or matters stated in any resolution, certificate, statement, instrument, opinion, report, notice, request, consent, order, approval, bond, Note, note or other paper or document, but the Trustee, in its discretion, may make such further inquiry or investigation into such facts or matters as it may see fit.

(g) The Trustee shall be under no obligation to exercise any of the rights or powers vested in it by this Indenture at the request, order or direction of any of the Noteholders pursuant to the provisions of this Indenture, unless such Noteholders shall have offered to the Trustee reasonable security or indemnity against the costs, expenses and liabilities which may be incurred therein or thereby.

(h) The rights, privileges, protections, immunities and benefits given to the Trustee, including, without limitation, its rights to be indemnified, are extended to, and shall be enforceable by, the Trustee in each of its capacities hereunder, and to each agent, custodian and other Person employed to act hereunder.

(i) The Trustee may request that the Company deliver an Officer's Certificate setting forth the names of individuals and/or titles of officers authorized at such time to take specified actions pursuant to this Indenture, which Officer's Certificate may be signed by any person authorized to sign an Officer's Certificate, including any person specified as so authorized in any such certificate previously delivered and not superseded.

(j) The permissive rights of the Trustee enumerated herein shall not be construed as duties.

SECTION 7.03. Individual Rights of Trustee. The Trustee in its individual or any other capacity may become the owner or pledgee of Notes and may otherwise deal with the Company or its Affiliates with the same rights it would have if it were not Trustee. Any conversion agent, Paying Agent, Registrar or co-paying agent may do the same with like rights. However, the Trustee must comply with Sections 7.10 and 7.11.

SECTION 7.04. Trustee's Disclaimer. The Trustee shall not be responsible for and makes no representation as to the validity or adequacy of this Indenture or the Notes, it shall not be accountable for the Company's use of the proceeds from the Notes, and it shall not be responsible for any statement of the Company in this Indenture or in any document issued in connection with the sale of the Notes or in the Notes other than the Trustee's certificate of authentication.

SECTION 7.05. Notice of Defaults. (a) The Trustee shall not be deemed to have notice of any Default, other than a payment default, unless a Trust Officer shall have been advised in writing that a Default has occurred. No duty imposed upon the Trustee in this Indenture shall be applicable with respect to any Default of which the Trustee is not deemed to have notice.

(b) If a Default occurs and is continuing and if it is known to the Trustee, the Trustee shall deliver to each Noteholder notice of the Default within 90 calendar days after it is known to a Trust Officer or written notice of it is received by the Trustee. Except in the case of a Default in payment of Principal, premium (if any) or interest on any Note (including payments pursuant to the redemption provisions of such Note), the Trustee may withhold notice if and so long as a committee of its Trust Officers in good faith determines that withholding notice is in the interests of the Noteholders.

SECTION 7.06. Reports by Trustee to Noteholders. As promptly as practicable after each August 15, beginning with August 15, 2007, and in any event prior to December 31 in each subsequent year, the Trustee shall, to the extent that any of the events described in TIA § 313(a) occurred within the previous twelve months, but not otherwise, deliver to each Noteholder a brief report dated as of August 15 that complies with Section 313(a) of the TIA. The Trustee shall also comply with Section 313(b) of the TIA.

SECTION 7.07. Compensation and Indemnity. The Company shall pay to the Trustee from time to time such compensation as the Company and the Trustee shall from time to time agree in writing. The Trustee's compensation shall not be limited by any law on compensation of a trustee of an express trust. The Company shall reimburse the Trustee upon request for all reasonable out-of-pocket expenses incurred or made by it, including costs of collection, in addition to the compensation for its services. Such expenses shall include the reasonable compensation and expenses, disbursements and advances of the Trustee's agents, counsel, accountants and experts. The Company shall indemnify the Trustee, and hold it harmless, against any and all loss, liability or expense (including reasonable attorneys' fees) incurred by or in connection with the offer and sale of the Notes or the administration of this trust and the performance of its duties hereunder. The Trustee shall notify the Company of any claim for which it may seek indemnity promptly upon obtaining actual knowledge thereof; provided, however, that any failure so to notify the Company shall not relieve the Company of its indemnity obligations hereunder. The Company shall defend the claim and the indemnified party shall provide reasonable cooperation at the Company's expense in the defense. Such indemnified parties may have separate counsel and the Company, as applicable, shall pay the fees and expenses of such counsel; provided, however, that the Company shall not be required to pay such fees and expenses if it assumes such indemnified parties' defense and, in such indemnified parties' reasonable judgment, there is no conflict of interest between the Company, as applicable, and such parties in connection with such defense. The Company need not reimburse any expense or indemnify against any loss, liability or expense incurred by an indemnified party through such party's own willful misconduct and negligence.

To secure the Company's payment obligations in this Section if the Company fails to compensate or indemnify the Trustee and to pay or reimburse the Trustee for expenses, disbursements and advances under this Section 7.07, the Trustee shall have a lien prior to the Notes on all money or property held or collected by the Trustee other than money or property held in trust to pay principal of and interest and any liquidated damages on particular Notes.

The Company's payment obligations pursuant to this Section shall survive the satisfaction or discharge of this Indenture, any rejection or termination of this Indenture under any Bankruptcy Law or the resignation or removal of the Trustee. When the Trustee incurs expenses after the occurrence of a Default specified in Section 6.01(g) or (h) with respect to the Company, the expenses are intended to constitute expenses of administration under the Bankruptcy Law.

SECTION 7.08. Replacement of Trustee. The Trustee may resign at any time by so notifying the Company. The Holders of a majority in Principal amount of the Notes may remove the Trustee by so notifying the Company and the Trustee and may appoint a successor Trustee. The Company shall remove the Trustee if:

- (a) the Trustee fails to comply with Section 7.10;
- (b) the Trustee is adjudged bankrupt or insolvent;
- (c) a receiver or other public officer takes charge of the Trustee or its property; or

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- (d) the Trustee otherwise becomes incapable of acting.

If the Trustee resigns, is removed by the Company or by the Holders of a majority in Principal amount of the Notes and such Noteholders do not reasonably promptly appoint a successor Trustee, or if a vacancy exists in the office of Trustee for any reason (the Trustee in such event being referred to herein as the retiring Trustee), the Company shall promptly appoint a successor Trustee.

A successor Trustee shall deliver a written acceptance of its appointment to the retiring Trustee and to the Company. Thereupon the resignation or removal of the retiring Trustee shall become effective, and the successor Trustee shall have all the rights, powers and duties of the Trustee under this Indenture. The successor Trustee shall deliver a notice of its succession to Noteholders. The retiring Trustee shall promptly transfer all property held by it as Trustee to the successor Trustee, subject to the lien provided for in Section 7.07.

If a successor Trustee does not take office within 60 days after the retiring Trustee resigns or is removed, the retiring Trustee or the Holders of 10% in Principal amount of the Notes may petition any court of competent jurisdiction for the appointment of a successor Trustee.

If the Trustee fails to comply with Section 7.10, any Noteholder may petition any court of competent jurisdiction for the removal of the Trustee and the appointment of a successor Trustee.

Notwithstanding the replacement of the Trustee pursuant to this Section, the Company's obligations under Section 7.07 shall continue for the benefit of the retiring Trustee.

SECTION 7.09. Successor Trustee by Merger. If the Trustee consolidates with, merges or converts into, or transfers all or substantially all of its corporate trust business or assets to, another corporation or banking association, the resulting, surviving or transferee corporation without any further act shall be the successor Trustee; provided that such corporation shall be eligible under the provisions of Section 7.10.

In case at the time such successor or successors by merger, conversion or consolidation to the Trustee shall succeed to the trusts created by this Indenture any of the Notes shall have been authenticated but not delivered, any such successor to the Trustee may adopt the certificate of authentication of any predecessor trustee, and deliver such Notes so authenticated; and in case at that time any of the Notes shall not have been authenticated, any successor to the Trustee may authenticate such Notes either in the name of any predecessor hereunder or in the name of the successor to the Trustee; and in all such cases such certificates shall have the full force that is provided in the Notes or in this Indenture; provided that the right to adopt the certificate of authentication of

any Trustee or authenticate Notes in the name of any predecessor Trustee shall apply only to its successor or successors by merger, conversion or consolidation.

SECTION 7.10. Eligibility; Disqualification. The Trustee shall at all times satisfy the requirements of TIA § 310(a). The Trustee shall have a combined capital and surplus of at least \$100,000,000 as set forth in its most recent published annual report of condition. The Trustee shall comply with TIA § 310(b); provided, however, that there shall be excluded from the operation of TIA § 310(b)(1) any indenture or indentures under which other securities or

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certificates of interest or participation in other securities of the Company are outstanding if the requirements for such exclusion set forth in TIA § 310(b)(1) are met.

SECTION 7.11. Preferential Collection of Claims Against Company. The Trustee shall comply with TIA § 311(a), excluding any creditor relationship listed in TIA § 311(b). A Trustee who has resigned or been removed shall be subject to TIA § 311(a) to the extent indicated.

ARTICLE 8

DISCHARGE OF INDENTURE

SECTION 8.01. Discharge of Liability on Notes. (a) When (i) the Company delivers to the Trustee all outstanding Notes (other than Notes replaced pursuant to Section 2.09) for cancellation or (ii) all outstanding Notes have become due and payable, whether at maturity or as a result of the delivery of a notice of redemption or upon a repurchase pursuant to Article 3 hereof, and the Company irrevocably deposits with the Trustee money sufficient to pay at maturity or upon redemption or repurchase all outstanding Notes, including interest thereon to maturity or such redemption or repurchase date (other than Notes replaced pursuant to Section 2.09), and any shares of Common Stock or other property due in respect of converted Notes, and if in each such case the Company pays all other sums payable hereunder by the Company, then this Indenture shall, subject to Section 8.01(b), cease to be of further effect. The Trustee shall acknowledge satisfaction and discharge of this Indenture on demand of the Company accompanied by an Officer's Certificate and, if requested, an Opinion of Counsel, and at the cost and expense of the Company.

(b) Notwithstanding clause (a) above, the Company's obligations in Sections 2.05, 2.06, 2.07, 2.08, 2.09, 2.10, 7.07, 7.08 and in this Article 8 shall survive until the Notes have been paid in full. Thereafter, the Company's obligations in Sections 7.07, 8.03 and 8.04 shall survive.

SECTION 8.02. Application of Trust Money. The Trustee shall hold in trust money and any shares of Common Stock or other property due in respect of converted Notes deposited with it pursuant to this Article 8. It shall apply the deposited money through the Paying Agent and in accordance with this Indenture to the payment of Principal of and interest on the Notes or, in the case of any shares of Common Stock or other property due in respect of converted Notes, in accordance with this Indenture in relation to the conversion of Notes pursuant to the terms hereof. Money and securities so held in trust are not subject to Article 12.

SECTION 8.03. Repayment to Company. The Trustee and the Paying Agent shall promptly turn over to the Company upon request any excess money or securities held by them at any time.

Subject to any applicable abandoned property law, the Trustee and the Paying Agent shall pay to the Company upon written request any money held by them for the payment of principal or interest and any shares of Common Stock or other property due in respect of converted Notes

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that remains unclaimed for two years, and, thereafter, Noteholders entitled to the money and/or securities must look to the Company for payment as general creditors.

SECTION 8.04. Reinstatement. If the Trustee or Paying Agent is unable to apply any money or to deliver any shares of Common Stock or other property due in respect of converted Notes in accordance with this Article 8 by reason of any legal proceeding or by reason of any order or judgment of any court or governmental authority enjoining, restraining or otherwise prohibiting such application, the Company's obligations under this Indenture and the Notes shall be revived and reinstated as though no deposit had occurred pursuant to this Article 8 until such time as the Trustee or Paying Agent is permitted to apply all such money and any shares of Common Stock or other property due in respect of converted Notes in accordance with this Article 8; provided, however, that, if the Company has made any payment of interest on or principal of any Notes because of the reinstatement of its obligations, the Company shall be subrogated to the rights of the Noteholders of such Notes to receive such payment from the money held by the Trustee or Paying Agent.

ARTICLE 9

AMENDMENTS

SECTION 9.01. Without Consent of Noteholders. The Company and the Trustee may amend this Indenture or the Notes without notice to or consent of any Noteholder:

(a) to provide for conversion rights of Noteholders and the Company's repurchase obligations in connection with a Fundamental Change in the event of any reclassification of the Common Stock, merger or consolidation, or sale, conveyance, transfer or lease of the Company's property and assets substantially as an entirety;

(b) to secure the Notes;

(c) to provide for the assumption of the Company's obligations in the event of a merger or consolidation, or sale, conveyance, transfer or lease of the Company's property and assets substantially as an entirety;

(d) to surrender any right or power conferred upon the Company;

(e) to add to the covenants of the Company for the benefit of the Noteholders;

(f) to cure any ambiguity or correct or supplement any inconsistent or otherwise defective provision contained in this Indenture; provided that such modification or amendment does not adversely affect the interests of the Noteholders in any material respect; provided, further, that any amendment made solely to conform the provisions of this Indenture to the description of the Notes contained in the offering memorandum relating to the Notes will not be deemed to adversely affect the interests of the Noteholders;

(g) to make any provision with respect to matters or questions arising under this Indenture that the Company may deem necessary or desirable and that shall not be

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inconsistent with provisions of this Indenture; provided that such change or modification does not, in the good faith opinion of the Board of Directors, adversely affect the interests of the Noteholders in any material respect;

(h) to provide for uncertificated Notes in addition to or in place of certificated Notes; provided, however, that the uncertificated Notes are issued in registered form for purposes of Section 163(f) of the Code or in a manner such that the uncertificated Notes are described in Section 163(f)(2)(B) of the Code;

(i) to increase the conversion rate; provided, that the increase will not adversely affect the interests of the Noteholders;

(j) to make any change in Article 12 that would limit or terminate the benefits available to any holder of Senior Indebtedness (or Representatives therefor) under Article 12;

(k) to comply with any requirements of the SEC in connection with qualifying, or maintaining the qualification of, this Indenture under the TIA;

(l) to add Guarantees with respect to the Notes;

(m) to make any changes or modifications necessary in connection with the registration of the Notes under the Securities Act as contemplated in the Registration Rights Agreement; provided that such change or modification does not adversely affect the interests of the Noteholders in any material respect; or

(n) to provide for a successor Trustee.

An amendment under this Section may not make any change that adversely affects the rights under Article 12 of any holder of Senior Indebtedness then outstanding unless the holders of such Senior Indebtedness (or any group or representative thereof authorized to give a consent) consent to such change.

After an amendment under this Section becomes effective, the Company shall deliver to Noteholders a notice briefly describing such amendment. The failure to give such notice to all Noteholders, or any defect therein, shall not impair or affect the validity of an amendment under this Section.

SECTION 9.02. With Consent of Noteholders. The Company and the Trustee may amend this Indenture or the Notes with the written consent of the Holders of at least a majority in Principal amount of the Notes then outstanding (including consents obtained in connection with a tender offer or exchange offer for the Notes), without notice to any other Noteholder. However, without the consent of each Holder of an outstanding Note affected, an amendment may not:

(a) reduce the principal amount of Notes whose Noteholders must consent to an amendment;

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(b) reduce the rate of or extend the time for payment of interest (including Additional Interest, if any) on any Note;

(c) reduce the Principal amount of or extend the Stated Maturity of any Note;

(d) reduce the amount payable upon redemption or repurchase of the Notes in accordance with Article 3;

(e) make any Note payable in currency other than that stated in the Note;

(f) impair the right of a holder to institute suit for payment of any Notes;

(g) affect the right of a holder to convert any Notes into shares of Common Stock (or, if we so elect, cash or a combination of cash and shares of Common Stock) or reduce the amount of cash, number of shares of Common Stock or any other property receivable upon conversion pursuant to the terms of this Indenture, or reduce the Conversion Rate, except as otherwise permitted pursuant to this Indenture;

- (h) change the redemption provisions in a manner adverse to the Noteholders;
- (i) change the Company's obligation to repurchase any Notes at the option of the Noteholder in a manner adverse to the Noteholders;
- (j) change the Company's obligation to repurchase any Notes upon a Fundamental Change in a manner adverse to the Noteholders;
- (k) reduce the number of Additional Shares to which a Noteholder would be entitled upon conversion in connection with a Non-Stock Change of Control;
- (l) modify Article 12 of this Indenture in a manner that materially adversely affects the Noteholders;
- (m) reduce the percentage of the Notes required for consent to any modification of the indenture that does not require the consent of each affected Noteholder; or
- (n) make any change in Section 6.04 or 6.07 or the second sentence of this Section 9.02.

It shall not be necessary for the consent of the Noteholders under this Section to approve the particular form of any proposed amendment, but it shall be sufficient if such consent approves the substance thereof.

An amendment under this Section 9.02 may not make any change that adversely affects the rights under Article 12 of any holder of Senior Indebtedness then outstanding unless the holders of such Senior Indebtedness (or any group or representative thereof authorized to give a consent) consent to such change.

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After an amendment under this Section becomes effective, the Company shall deliver to Noteholders a notice briefly describing such amendment. The failure to give such notice to all Noteholders, or any defect therein, shall not impair or affect the validity of an amendment under this Section.

SECTION 9.03. Compliance with Trust Indenture Act. Every amendment to this Indenture or the Notes shall comply with the TIA as then in effect.

SECTION 9.04. Revocation and Effect of Consents and Waivers. A consent to an amendment or a waiver by a Noteholder of a Note shall bind the Noteholder and every subsequent Noteholder of that Note or portion of the Note that evidences the same debt as the consenting Noteholder's Note, even if notation of the consent or waiver is not made on the Note. However, any such Noteholder or subsequent Noteholder may revoke the consent or waiver as to such Noteholder's Note or portion of the Note if the Trustee receives the notice of revocation before the date the amendment or waiver becomes effective. After an amendment or waiver becomes effective, it shall bind every Noteholder. An amendment or waiver becomes effective once both (i) the requisite number of consents have been received by the Company or the Trustee and (ii) such amendment or waiver has been executed by the Company and the Trustee.

The Company may, but shall not be obligated to, fix a record date for the purpose of determining the Noteholders entitled to give their consent or take any other action described above or required or permitted to be taken pursuant to this Indenture. If a record date is fixed, then notwithstanding the immediately preceding paragraph, those Persons who were Noteholders at such record date (or their duly designated proxies), and only those Persons, shall be entitled to give such consent or to revoke any consent previously given or to take any such action, whether or not such Persons continue to be Noteholders after such record date. No such consent shall be valid or effective for more than 120 days after such record date.

SECTION 9.05. Notation on or Exchange of Notes. If an amendment changes the terms of a Note, the Trustee may require the Noteholder of the Note to deliver it to the Trustee. The Trustee may place an appropriate notation on the Note regarding the changed terms and return it to the Noteholder. Alternatively, if the Company or the Trustee so determines, the Company in exchange for the Note shall issue and the Trustee shall authenticate a new Note that reflects the changed terms. Failure to make the appropriate notation or to issue a new Note shall not affect the validity of such amendment.

SECTION 9.06. Trustee to Sign Amendments. The Trustee shall sign any amendment authorized pursuant to this Article 9 if the amendment does not adversely affect the rights, duties, liabilities or immunities of the Trustee. If it does, the Trustee may but need not sign it. In signing such amendment the Trustee shall be entitled to receive, and (subject to Section 7.01) shall be fully protected in relying upon, in addition to the documents required by Section 13.04, an Officer's Certificate and, if requested, an Opinion of Counsel, stating that such amendment is authorized or permitted by this Indenture and that such amendment is the legal, valid and binding obligation of the Company enforceable against it in accordance with its terms, subject to customary exceptions, and complies with the provisions hereof (including Section 9.03).

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ARTICLE 10

CONVERSION OF NOTES

SECTION 10.01. Right to Convert. (a) Subject to and upon compliance with the provisions of this Indenture, on or prior to the close of business on the Trading Day immediately preceding the Maturity Date, any Noteholder whose Note has not been previously redeemed or repurchased shall have the right, at such Noteholder's option, to convert the Principal amount of the Notes held by such holder, or any portion of such principal amount which is an integral multiple of \$1,000, into at the Company's option shares of Common Stock, cash or a combination of cash and shares of Common Stock (as such shares shall then be constituted) as described in Section 10.12, subject to Section 10.14, at the Conversion Rate in effect at such time, by surrender of the Notes so to be converted in whole or in part, together with any required funds, under the circumstances described in this Section 10.01 and in the manner provided in Section 10.02. The Notes shall be convertible only upon the occurrence of one of the following events:

(1) prior to February 15, 2025 on any date during any Fiscal Quarter beginning after March 31, 2007 (and only during such Fiscal Quarter), if the Closing Sale Price of a share of Common Stock was more than 120% of the then current Conversion Price for at least 20 Trading Days in the 30 consecutive Trading-Day period ending on the last Trading Day of the immediately preceding Fiscal Quarter;

(2) on or after February 15, 2025;

(3) with respect to the Notes called for redemption pursuant to Section 3.01, until 5:00 p.m., New York City time, on the Business Day prior to the relevant redemption date even if the Notes are not otherwise convertible at such time, after which time the right to convert the Notes shall expire unless the Company defaults in the payment of the redemption price;

(4) if the Company distributes to all or substantially all holders of Common Stock rights or warrants (other than pursuant to a shareholder rights plan) entitling them to purchase, for a period of 45 calendar days or less, Common Stock at less than the average Closing Sale Price per share of the Common Stock for the 10 Trading Days preceding the declaration date for such distribution;

(5) if the Company distributes to all or substantially all holders of Common Stock, cash or other assets, debt securities or rights to purchase the Company's securities (other than pursuant to a shareholder rights plan, share split of Common Stock or a dividend or distribution on its Common Stock in shares of Common Stock), which distribution has a per share value as determined by the Board of Directors exceeding 5% of the Closing Sale Price per share of the Common Stock on the Trading Day preceding the declaration for such distribution;

(6) if a Fundamental Change occurs, at any time beginning on the effective date of the Fundamental Change until 5:00 p.m., New York City time, on the date that

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is 15 calendar days after the actual effective date, or, if applicable, on the Business Day preceding the Fundamental Change Repurchase Date relating to such Fundamental Change; or

(7) during the five consecutive Business-Day period following any five consecutive Trading-Day period in which the Trading Price per \$1,000 principal amount of the Notes was less than 98% of the product of (x) the Closing Sale Price of a share of Common Stock and (y) the applicable Conversion Rate for each day of such five consecutive Trading Day period.

(b) (1) The Company shall notify the Trustee in writing on or prior to the fifth Business Day following the first day of each Fiscal Quarter (commencing prior to February 15, 2025, beginning with the Fiscal Quarter ending June 30, 2007) whether the condition to conversion set forth in Section 10.01(a)(1) above shall have been satisfied with respect to such Fiscal Quarter.

(2) The Trustee shall have no obligation to determine the Trading Price of the Notes and whether the Notes are convertible pursuant to clause (7) of Section 10.01(a) unless the Company has requested such determination; and the Company shall have no obligation to make such request unless a Noteholder makes a request for a determination and provides the Company with reasonable evidence that the Trading Price per \$1,000 principal amount of Notes is reasonably likely to be less than 98% of the product of the Closing Sale Price of the Common Stock and the Conversion Rate then in effect per \$1,000 principal amount of Notes. At such time, the Company shall instruct the Trustee to determine the Trading Price of the Notes beginning on the next Trading Day and on each successive Trading Day for 10 consecutive Trading Days to determine whether the Trading Prices for the Notes for each Trading Day in any five consecutive Trading Day period within such 10-Trading Day period is less than 98% of the product of the Closing Sale Price of the Common Stock and the then current Conversion Rate, and to notify the Company accordingly.

The Trustee shall be entitled at its sole discretion to consult with the Company and to request the assistance of the Company in connection with the Trustee's duties and obligations pursuant to Section 10.01(b)(2) hereof (including the calculation or determination of the Trading Price), and the Company agrees, if requested by the Trustee, to cooperate with, and provide assistance to, the Trustee in carrying out its duties under this Section 10.01. Upon any determination or calculation made by the Trustee in carrying out its duties under this Section 10.01, the Trustee shall notify the Company in writing of such determination, and the Company shall promptly confirm such determination in writing to the Trustee.

(c) In the case of a distribution contemplated by clauses (4) or (5) of Section 10.01(a), the Company shall notify Noteholders at least 20 calendar days prior to the ex-dividend date (the first date on which the Common Stock trades on the relevant market from which the Closing Sale Price was obtained without the right to receive such right, warrant, dividend or distribution) for such distribution (the "**Distribution Notice**"). Once the Company has given the Distribution Notice, Noteholders may surrender their Notes for conversion at any time until the earlier of (i) 5:00 p.m., New York City time, on the Business Day immediately preceding the ex-dividend date or (ii) the Company's announcement that such distribution will not take place. In the event of a distribution contemplated by clauses (4) or (5) of Section 10.01(a), Noteholders

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may not convert the Notes if the Noteholders may otherwise participate in such distribution without converting their Notes. The Company will provide written notice to the Trustee and Noteholders and any conversion agent as soon as reasonably practicable of any anticipated or actual event or transaction that will cause or causes the Notes to become convertible pursuant to clauses (4) or (5) of Section 10.01(a).

(d) In addition, if the Company consolidates with or merges with or into another Person or is a party to a binding share exchange or conveys, transfers, sells, leases or otherwise disposes of all or substantially all of its properties and assets in each case, pursuant to which the Common Stock would be converted into cash, securities and/or other property, then the Noteholders shall have the right to convert their Notes at any time from and after the date that is 15 calendar days prior to the anticipated effective date of the transaction until, but excluding, the date that is 15 calendar days after the actual effective date of such transaction unless the transaction also constitutes a Fundamental Change.

The Board of Directors shall determine the anticipated effective date of the transaction, and such determination shall be conclusive and binding on the Noteholders and shall be publicly announced by the Company and posted on its website not later than 20 calendar days prior to the anticipated effective date.

(e) Whenever the Notes shall become convertible pursuant to this Section 10.01, the Company or, at the Company's request, the Trustee in the name and at the expense of the Company, shall notify the Noteholders of the event triggering such convertibility in the manner provided in Section 13.02, and the Company shall also publicly announce such information and publish it on the Company's website. Any notice so given shall be conclusively presumed to have been duly given, whether or not the Noteholder receives such notice. The Company shall notify Noteholders at least 20 calendar days prior to the anticipated effective date of any Fundamental Change.

(f) Notes in respect of which a Noteholder has delivered a Repurchase Notice exercising such Noteholder's right to require the Company to repurchase such Notes pursuant to Section 3.04 or 3.05 may be converted only if such Repurchase Notice is withdrawn in accordance with Section 3.07 prior to 5:00 p.m., New York City time, on the Business Day immediately preceding the Repurchase Date or the Fundamental Change Repurchase Date, as applicable. If a Noteholder fails to withdraw a Repurchase Notice, such Noteholders' conversion rights with respect to the Notes so subject to repurchase will expire at 5:00 p.m., New York City time, on the Business Day preceding the Repurchase Date or the Fundamental Change Repurchase Date, unless the Company defaults in payment of the repurchase price.

(g) A Noteholder is not entitled to any rights of a holder of Common Stock until such holder has converted his Notes to Common Stock, and only to the extent such Notes are deemed to have been converted to Common Stock under this Article 10.

SECTION 10.02. Exercise of Conversion Right; Issuance of Common Stock on Conversion; No Adjustment for Interest or Dividends. In order to exercise the conversion right with respect to any Notes in certificated form, the Company must receive at the office or agency of the Company maintained for that purpose or, at the option of such Noteholder, the Corporate

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Trust Office, such Notes with the original or facsimile of the form entitled "**Conversion Notice**" on the reverse thereof, duly completed and manually signed, together with such Notes duly endorsed for transfer, together with any other required transfer documents, accompanied by the funds, if any, required by this Section 10.02. Such notice shall also state the name or names (with address or addresses) in which the certificate or certificates for shares of Common Stock which shall be issuable on such conversion shall be issued, and shall be accompanied by transfer or similar taxes, if required pursuant to Section 10.07.

In order to exercise the conversion right with respect to any interest in a Global Note, the Noteholder must (i) complete, or cause to be completed, the appropriate instruction form for conversion pursuant to the Depository's book-entry conversion program, (ii) deliver, or cause to be delivered, by book-entry delivery an interest in such Global Note, (iii) furnish appropriate endorsements and transfer documents if required by the Company or the Trustee or conversion agent and (iv) pay the funds, if any, required by this Section 10.02 and any transfer or similar taxes if required pursuant to Section 10.07.

The certificate or certificates for the number of full shares of Common Stock into which the Notes are converted (and cash in lieu of fractional shares) and cash, if applicable, will be delivered to such Noteholder after satisfaction of the requirements for conversion set forth above, in accordance with Section 10.12. In case any Notes of a denomination greater than \$1,000 shall be surrendered for partial conversion, and subject to Section 2.03, the Company shall execute and the Trustee shall authenticate and deliver to the Noteholder so surrendered, without charge to the Noteholder, a new Note or Notes in authorized denominations in an aggregate principal amount equal to the unconverted portion of the surrendered Notes.

Each conversion shall be deemed to have been effected as to any such Notes (or portion thereof) on the date on which the requirements set forth above in this Section 10.02 have been satisfied as to such Notes (or portion thereof) (the "**Conversion Date**") and such Notes will be deemed to have been converted immediately prior to 5:00 p.m., New York City time, on the Conversion Date. The Person in whose name any certificate or certificates for shares of Common Stock shall be issuable upon such conversion shall be deemed to have become, on said date, the holder of record of the shares represented thereby; provided that any such surrender on any date when the stock transfer books of the Company shall be closed shall constitute the Person in whose name the certificates are to be issued as the record holder thereof for all purposes on the next succeeding day on which such stock transfer books are open, but such conversion shall be at the Conversion Rate in effect on the Conversion Date.

Any Notes or portion thereof surrendered for conversion during the period from 5:00 p.m., New York City time, on the Record Date for any interest payment date to 5:00 p.m., New York City time, on the Business Day preceding the applicable interest payment date shall be accompanied by payment, in immediately available funds or other funds acceptable to the Company, of an amount equal to the interest (excluding any Additional Interest) otherwise payable on such interest payment date on the principal amount being converted; provided that no such payment need be made (1) if a Noteholder converts its Notes in connection with a redemption and the Company has specified a redemption date that is after a Record Date and on or prior to the corresponding interest payment date, (2) if a Noteholder converts its Notes in connection with a Fundamental Change and the Company has specified a Fundamental Change

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Repurchase Date that is after a Record Date and on or prior to the corresponding interest payment date or (3) to the extent of any overdue interest, if any overdue interest exists at the time of conversion with respect to such Notes. Except as provided above in this Section 10.02 and Section 10.05, no payment or other adjustment shall be made for interest accrued on any Notes converted or for dividends on any shares issued upon the conversion of such Notes as provided in this Article 10.

Upon the conversion of an interest in a Global Note, the Trustee (or other conversion agent appointed by the Company), or the custodian for the Global Note at the direction of the Trustee (or other conversion agent appointed by the Company), shall make a notation on such Global Note as to the reduction in the principal amount represented thereby. The Company shall notify the Trustee in writing of any conversions of Notes effected through any conversion agent other than the Trustee.

Upon the conversion of any Notes, the accrued but unpaid interest attributable to the period from the issue date of the Notes to the Conversion Date, with respect to the converted Notes, shall not be cancelled, extinguished or forfeited, but rather shall be deemed to be paid in full to the Noteholder thereof through delivery of the cash (including a cash payment in lieu of fractional shares, if any) and shares of Common Stock, if any, in exchange for the Notes being converted pursuant to the provisions hereof.

SECTION 10.03. Cash Payments in Lieu of Fractional Shares. No fractional shares of Common Stock or scrip certificates representing fractional shares shall be issued upon conversion of Notes. If more than one Note shall be surrendered for conversion at one time by the same Noteholder, the number of full shares that shall be issuable upon conversion shall be computed on the basis of the aggregate Principal amount of the Notes (or specified portions thereof to the extent permitted hereby) so surrendered. If any fractional share of stock would be issuable upon the conversion of any Note or Notes, the Company shall make an adjustment and payment therefor in cash to the Noteholder at a price equal to the Closing Sale Price on the last Trading Day immediately preceding the Conversion Date.

SECTION 10.04. Conversion Rate.

(a) Each \$1,000 principal amount of the Notes shall be convertible into cash and the number of shares of Common Stock, if any, based upon the Conversion Rate which is specified in the form of Notes attached as Exhibit A hereto, subject to adjustment as provided in this Section 10.04 and Section 10.05.

(b) Subject to Section 10.13, if and only to the extent a Noteholder elects to convert Notes at any time following the date on which a Non-Stock Change of Control becomes effective (the “**Effective Date**”) but before 5:00 p.m., New York City time, on the Business Day immediately preceding the related Fundamental Change Purchase Date, the Company shall increase the Conversion Rate applicable to such converted Notes by a number of additional shares of Common Stock (the “**Additional Shares**”) as set forth below. The number of Additional Shares of Common Stock shall be determined by reference to the table below, based on the Effective Date and the price (the “**Stock Price**”) paid per share for the Common Stock in the Non-Stock Change of Control. If holders of Common Stock receive only cash in the Non-Stock

Change of Control, the Stock Price shall be the cash amount paid per share. Otherwise, the Stock Price shall be the average of the Closing Sale Prices of the Common Stock on the five Trading Days prior to but not including the Effective Date of such Non-Stock Change of Control.

The numbers of Additional Shares of Common Stock set forth in the table below shall be adjusted as of any date on which the Conversion Rate is adjusted in the same manner in which the Conversion Rate is adjusted. The Stock Prices set forth in the table below shall be adjusted, as of any date on which the Conversion Rate is adjusted, to equal the Stock Price applicable immediately prior to such adjustment multiplied by a fraction, of which

- (1) the numerator shall be the Conversion Rate immediately prior to the adjustment and
- (2) the denominator shall be the Conversion Rate as so adjusted.

The following table sets forth the Stock Price and number of Additional Shares by which the Conversion Rate shall be adjusted:

<u>Effective Date</u>	<u>Stock Price</u>									
	<u>\$11.25</u>	<u>\$14.63</u>	<u>\$17.50</u>	<u>\$20.00</u>	<u>\$22.50</u>	<u>\$25.00</u>	<u>\$27.50</u>	<u>\$30.00</u>	<u>\$32.50</u>	<u>\$35.00</u>
January 23, 2007	20.5127	13.0547	9.5132	7.4761	6.0233	4.9498	4.1326	3.4953	2.9936	2.5831
February 15, 2008	20.1768	12.3913	8.7956	6.7783	5.3703	4.3510	3.5894	3.0049	2.5500	2.1854
February 15, 2009	19.4806	11.3692	7.7668	5.8165	4.4981	3.5720	2.8992	2.3952	2.0081	1.7084
February 15, 2010	18.3509	9.8224	6.2720	4.4661	3.3134	2.5468	2.0169	1.6369	1.3549	1.1417
February 15, 2011	16.5402	7.3061	3.9699	2.5152	1.7108	1.2417	0.9527	0.7627	0.6300	0.5322
February 15, 2012	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

If the Stock Price and Effective Date are not set forth on the table above and the Stock Price is:

(i) between two Stock Prices on the table or the Effective Date is between two date on the table, the number of Additional Shares of Common Stock shall be determined by the Trustee by straight-line interpolation between the number of Additional Shares set forth for the higher and lower Stock Price and the two Effective Dates, as applicable, based on a 360-day year;

(ii) in excess of \$35.00 per share (subject to adjustment), no Additional Shares shall be issued upon conversion; or

(iii) less than \$11.25 per share (subject to adjustment), no Additional Shares shall be issued upon conversion.

Notwithstanding the foregoing, in no event will the Conversion Rate as adjusted pursuant to this Section 10.04 exceed 88.8888 per \$1,000 principal amount of the Notes, subject to adjustments in the same manner as adjustments to the number of Additional Shares of Common Stock as set forth in this Section 10.04(b).

The Company shall provide written notice to all Noteholders and to the Trustee at least 20 calendar days prior to the anticipated Effective Date of a Non-Stock Change of Control. The

SECTION 10.05. Adjustment of Conversion Rate. The Conversion Rate shall be adjusted from time to time by the Company as follows:

(a) In case the Company shall, at any time or from time to time while any of the Notes are outstanding, pay a dividend in shares of Common Stock or make a distribution in shares of Common Stock to all holders of its outstanding shares of Common Stock, then the Conversion Rate in effect at the opening of business on the date following the Record Date fixed for the determination of stockholders entitled to receive such dividend or other distribution shall be increased by multiplying such Conversion Rate by a fraction:

(1) the numerator of which shall be the sum of the number of shares of Common Stock outstanding at the close of business on the date fixed for the determination of stockholders entitled to receive such dividend or other distribution plus the total number of shares of Common Stock constituting such dividend or other distribution; and

(2) the denominator of which shall be the number of shares of Common Stock outstanding at the close of business on the date fixed for such determination,

such increase to become effective immediately after the opening of business on the day following the date fixed for such determination. For the purpose of this paragraph (a), the number of shares of Common Stock at any time outstanding shall not include shares held in the treasury of the Company. The Company will not pay any dividend or make any distribution on shares of Common Stock held in the treasury of the Company. If any dividend or distribution of the type described in this Section 10.05(a) is declared but not so paid or made, the Conversion Rate shall again be adjusted to the Conversion Rate that would then be in effect if such dividend or distribution had not been declared.

(b) In case outstanding shares of Common Stock shall be subdivided into a greater number of shares of Common Stock, the Conversion Rate in effect at the opening of business on the day following the day upon which such subdivision becomes effective shall be proportionately increased, and conversely, in case outstanding shares of Common Stock shall be combined into a smaller number of shares of Common Stock, the Conversion Rate in effect at the opening of business on the day following the day upon which such combination becomes effective shall be proportionately reduced, such increase or reduction, as the case may be, to become effective immediately after the opening of business on the day following the day upon which such subdivision or combination becomes effective.

(c) In case the Company shall issue rights or warrants (other than any rights or warrants referred to in Section 10.05(d)) to all holders of its outstanding shares of Common Stock entitling them to subscribe or purchase, for a period of up to 45 calendar days, shares of Common Stock at a price per share less than the then Current Market Price, the Conversion Rate shall be increased so that the same shall equal the rate determined by multiplying the Conversion

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Rate in effect immediately prior to the date fixed for determination of stockholders entitled to receive such rights or warrants by a fraction,

(1) the numerator of which shall be the number of shares of Common Stock outstanding on the date fixed for determination of stockholders entitled to receive such rights or warrants plus the total number of Additional Shares of Common Stock offered for subscription or purchase, and

(2) the denominator of which shall be the sum of the number of shares of Common Stock outstanding at the close of business on the date fixed for determination of stockholders entitled to receive such rights or warrants plus the number of shares that the aggregate offering price of the total number of shares so offered would purchase at the Current Market Price on such date.

Such adjustment shall be successively made whenever any such rights or warrants are issued, and shall become effective immediately after the opening of business on the day following the date fixed for determination of stockholders entitled to receive such rights or warrants; provided, that no adjustment to the Conversion Rate shall be made if the Noteholder will otherwise participate in such distribution without conversion as a result of holding the Notes. To the extent that shares of Common Stock are not delivered after the expiration of such rights or warrants, the Conversion Rate shall be readjusted to the Conversion Rate that would then be in effect had the adjustments made upon the issuance of such rights or warrants been made on the basis of delivery of only the number of shares of Common Stock actually delivered. If such rights or warrants are not so issued, the Conversion Rate shall again be adjusted to be the Conversion Rate that would then be in effect if such date fixed for the determination of stockholders entitled to receive such rights or warrants had not been fixed. In determining whether any rights or warrants entitle the Noteholders to subscribe for or purchase shares of Common Stock at less than such Current Market Price, and in determining the aggregate offering price of such shares of Common Stock, there shall be taken into account any consideration received by the Company for such rights or warrants and any amount payable on exercise or conversion thereof, the value of such consideration, if other than cash, to be determined by the Board of Directors.

(d) In case the Company shall, by dividend or otherwise, distribute to all holders of its outstanding shares of Common Stock shares of any class of Capital Stock of the Company or evidences of its Indebtedness or assets (including securities, but excluding (i) any rights or warrants referred to in Section 10.05(c), (ii) any dividends or distributions in connection with a reclassification, consolidation, merger, combination or sale or conveyance to which Section 10.06 applies, (iii) any dividends or distributions paid exclusively in cash or (iv) any dividends or distributions referred to in Section 10.05(a)) (any of the foregoing hereinafter in this Section 10.05(d)) called the “**Distributed Assets**”), then, in each such case, the Conversion Rate shall be increased so that the same shall be equal to the rate determined by multiplying the Conversion Rate in effect on the record date with respect to such distribution by a fraction,

(1) the numerator of which shall be the Current Market Price on such record date; and

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(2) the denominator of which shall be the Current Market Price on such record date less the Fair Market Value (as determined by the Board of Directors, whose determination shall be conclusive, and described in a resolution of the Board of Directors) on the record date of the portion of the Distributed Assets so distributed applicable to one share of Common Stock,

such adjustment to become effective immediately prior to the opening of business on the day following such record date; provided that if the then Fair Market Value (as so determined) of the portion of the Distributed Assets so distributed applicable to one share of Common Stock is equal to or greater than the Current Market Price on the record date or the Current Market Price exceed such Fair Market Value by less than \$1.00, in lieu of the foregoing adjustment, adequate provision shall be made so that each Noteholder shall have the right to receive upon conversion the amount of Distributed Assets such Noteholder would have received had such Noteholder converted each Notes solely into Common Stock immediately prior to the record date; and provided, further, that no adjustment to the Conversion Rate shall be made if the Noteholder will otherwise participate in such distribution without conversion as a result of holding the Notes. If such dividend or distribution is not so paid or made, the Conversion Rate shall again be adjusted to be the Conversion Rate that would then be in effect if such dividend or distribution had not been declared.

If the Board of Directors determines the Fair Market Value of any distribution for purposes of this Section 10.05(d) by reference to the actual or when issued trading market for any Distributed Assets comprising all or part of such distribution, it must in doing so consider the prices in such market over the same period (the “**Reference Period**”) used in computing the Current Market Price pursuant to Section 10.05(h)(i) to the extent possible, unless the Board of Directors determines in good faith that determining the Fair Market Value during the Reference Period would not be in the best interest of the Noteholders. Notwithstanding the foregoing, in the event any such distribution consists of shares of Capital Stock of, or similar equity interests in, one or more of the Company’s Subsidiaries (a “**Spin-Off**”), the Conversion Rate shall be increased so that the same shall be equal to the rate determined by multiplying the Conversion Rate in effect immediately prior to the close of business on the record date with respect to such distribution by a fraction:

(3) the numerator of which shall be the Current Market Price of the Common Stock, plus the Fair Market Value of the portion of the Distributed Assets so distributed applicable to one share of Common Stock (determined on the basis of the number of shares of Common Stock outstanding on the record date), determined as set forth above, and

(4) the denominator of which shall be the Current Market Price on such record date, and

such increase to become effective immediately prior to the opening of business on the day following the last Trading Day of the Spin-Off Valuation Period (as defined below). In the event that such dividend or distribution is not so paid or made, the Conversion Rate shall again be adjusted to be the Conversion Rate that would then be in effect if such dividend or distribution had not been declared. In the case of a Spin-Off, the Fair Market Value of the securities to be

distributed shall equal the average of the Closing Sale Prices of such securities on the principal securities market on which such securities are traded for the five consecutive Trading Days commencing on and including the sixth day of trading of those securities after the effectiveness of the Spin-Off (the “**Spin-Off Valuation Period**”), and the Current Market Price shall be measured for the same period. In the event, however, that an underwritten initial public offering of the securities in the Spin-Off occurs simultaneously with the Spin-Off, Fair Market Value of the securities distributed in the Spin-Off shall mean the initial public offering price of such securities and the Current Market Price shall mean the Closing Sale Price for the Common Stock on the same Trading Day.

Rights or warrants distributed by the Company to all holders of Common Stock entitling the holders thereof to subscribe for or purchase shares of the Company’s Capital Stock (either initially or under certain circumstances), which rights or warrants, until the occurrence of a specified event or events (“**Trigger Event**”): (i) are deemed to be transferred with such shares of Common Stock; (ii) are not exercisable; and (iii) are also issued in respect of future issuances of Common Stock, shall be deemed not to have been distributed for purposes of this Section 10.05 (and no adjustment to the Conversion Rate under this Section 10.05 will be required) until the occurrence of the earliest Trigger Event, whereupon such rights and warrants shall be deemed to have been distributed and an appropriate adjustment (if any is required) to the Conversion Rate shall be made under this Section 10.05(d). If any such right or warrant, including any such existing rights or warrants distributed prior to the date of this Indenture, are subject to events, upon the occurrence of which such rights or warrants become exercisable to purchase different securities, evidences of indebtedness or other assets, then the date of the occurrence of any and each such event shall be deemed to be the date of distribution and record date with respect to new rights or warrants with such rights (and a termination or expiration of the existing rights or warrants without exercise by any of the holders thereof). In addition, in the event of any distribution (or deemed distribution) of rights or warrants, or any Trigger Event or other event (of the type described in the preceding sentence) with respect thereto that was counted for purposes of calculating a distribution amount for which an adjustment to the Conversion Rate under this Section 10.05 was made, (1) in the case of any such rights or warrants that shall all have been redeemed or repurchased without exercise by any holders thereof, the Conversion Rate shall be readjusted upon such final redemption or repurchase to give effect to such distribution or Trigger Event, as the case may be, as though it were a cash distribution, equal to the per share redemption or repurchase price received by a holder or holders of Common Stock with respect to such rights or warrants (assuming such holder had retained such rights or warrants), made to all holders of Common Stock as of the date of such redemption or repurchase, and (2) in the case of such rights or warrants that shall have expired or been terminated without exercise by any holders thereof, the Conversion Rate shall be readjusted as if such rights and warrants had not been issued.

No adjustment of the Conversion Rate shall be made pursuant to this Section 10.05(d) in respect of rights or warrants distributed or deemed distributed on any Trigger Event to the extent that such rights or warrants are actually distributed or reserved by the Company for distribution to Noteholders upon conversion by such Noteholders to Common Stock.

For purposes of this Section 10.05(d) and Sections 10.05(a) and (b), any dividend or distribution to which this Section 10.05(d) is applicable that also includes shares of Common

Stock, or rights or warrants to subscribe for or purchase shares of Common Stock (or both), shall be deemed instead to be (1) a dividend or distribution of the evidences of indebtedness, assets or shares of capital stock other than such shares of Common Stock or rights or warrants (and any Conversion Rate

adjustment required by this Section 10.05(d) with respect to such dividend or distribution shall then be made) immediately followed by (2) a dividend or distribution of such shares of Common Stock or such rights or warrants (and any further Conversion Rate adjustment required by Sections 10.05(a) or 10.05(b) with respect to such dividend or distribution shall then be made), except (A) the record date of such dividend or distribution shall be substituted as “the date fixed for the determination of stockholders entitled to receive such dividend or other distribution,” “the date fixed for the determination of stockholders entitled to receive such rights or warrants” and “the date fixed for such determination” within the meaning of Section 10.05(a) and 10.05(b) and (B) any shares of Common Stock included in such dividend or distribution shall not be deemed “outstanding at the close of business on the date fixed for such determination” within the meaning of Section 10.05(a).

(e) In case the Company shall, by dividend or otherwise, distribute to all holders of its Common Stock exclusively cash (including any quarterly cash dividend, but excluding (x) any dividend or distribution in connection with the liquidation, dissolution or winding up of the Company, whether voluntary or involuntary and (y) any dividend or distribution in connection with a reclassification, consolidation, merger, binding share exchange or sale to which Section 10.06 applies) then the Conversion Rate shall be increased so that the same shall equal the rate determined by multiplying the Conversion Rate in effect on the applicable record date by a fraction,

(1) the numerator of which shall be the Current Market Price on such record date; and

(2) the denominator of which shall be the Current Market Price on such record date less the amount per share of such dividend or distribution,

such adjustment to be effective immediately prior to the opening of business on the day following the record date; provided that if the portion of the cash so distributed applicable to one share of Common Stock is equal to or greater than the Current Market Price on the record date, in lieu of the foregoing adjustment, adequate provision shall be made so that each Noteholder shall have the right to receive upon conversion the amount of cash such Noteholder would have received had such Noteholder converted each Note solely into Common Stock immediately prior to the record date. If such dividend or distribution is not so paid or made, the Conversion Rate shall again be adjusted to be the Conversion Rate that would then be in effect if such dividend or distribution had not been declared.

(f) In case a tender or exchange offer made by the Company or any Subsidiary for all or any portion of the Common Stock shall expire and such tender or exchange offer (as amended upon the expiration thereof) shall require the payment to stockholders of consideration per share of Common Stock having a Fair Market Value (as determined by the Board of Directors, whose determination shall be conclusive and described in a resolution of the Board of Directors) that as of the last time (the “**Expiration Time**”) tenders or exchanges may be made pursuant to such tender or exchange offer (as it may be amended) exceeds the Closing

Sale Price of a share of Common Stock on the Trading Day next succeeding the Expiration Time, the Conversion Rate shall be increased so that the same shall equal the rate determined by multiplying the Conversion Rate in effect immediately prior to the Expiration Time by a fraction,

(1) the numerator of which shall be the sum of (x) the Fair Market Value (determined as aforesaid) of the aggregate consideration payable to stockholders based on the acceptance (up to any maximum specified in the terms of the tender or exchange offer) of all shares validly tendered or exchanged and not withdrawn as of the Expiration Time (the shares deemed so accepted up to any such maximum, being referred to as the “**Purchased Shares**”) and (y) the product of the number of shares of Common Stock outstanding (less any Purchased Shares) at the Expiration Time and the Closing Sale Price of a share of Common Stock on the Trading Day next succeeding the Expiration Time, and

(2) the denominator of which shall be the number of shares of Common Stock outstanding (including any Purchased Shares) at the Expiration Time multiplied by the Closing Sale Price of a share of Common Stock on the Trading Day next succeeding the Expiration Time,

such adjustment to become effective immediately prior to the opening of business on the day following the Expiration Time. If the Company is obligated to purchase shares pursuant to any such tender or exchange offer, but the Company is permanently prevented by applicable law from effecting any such purchases or all such purchases are rescinded, the Conversion Rate shall again be adjusted to be the Conversion Rate that would then be in effect if such tender or exchange offer had not been made.

(g) For purposes of this Section 10.05, the following terms shall have the meaning indicated:

(i) “**Current Market Price**” on any date means the average of the daily Closing Sale Prices per share of Common Stock for the ten consecutive Trading Days immediately prior to such date (the “**day in question**”); provided that if:

(1) the “ex” date (as hereinafter defined) for any event (other than the issuance or distribution requiring such computation) that requires an adjustment to the Conversion Rate pursuant to Section 10.05 (a), (b), (c), (d), (e) or (f) occurs during such ten consecutive Trading Days, the Closing Sale Price for each Trading Day prior to the “ex” date for such other event shall be adjusted by dividing such Closing Sale Price by the same fraction by which the Conversion Rate is so required to be multiplied as a result of such other event;

(2) the “ex” date for any event (other than the issuance or distribution requiring such computation) that requires an adjustment to the Conversion Rate pursuant to Section 10.05(a), (b), (c), (d), (e) or (f) occurs on or after the “ex” date for the issuance or distribution requiring such computation and prior to the day in question, the Closing Sale Price for each Trading Day on and after the “ex” date for such other event shall be adjusted by multiplying such Closing Sale Price by the fraction by

which the Conversion Rate is so required to be multiplied as a result of such other event; and

(3) the “ex” date for the issuance or distribution requiring such computation is prior to the day in question, after taking into account any adjustment required pursuant to clause (1) or (2) of this proviso, the Closing Sale Price for each Trading Day on or after such “ex” date shall be adjusted by adding thereto the amount of any cash and the Fair Market Value (as determined by the Board of Directors in a manner consistent with any determination of such value for purposes of Section 10.05(d), (e) or (f)) of the evidences of indebtedness, shares of capital stock or assets being distributed applicable to one share of Common Stock as of the close of business on the day before such “ex” date.

Notwithstanding the foregoing, whenever successive adjustments to the Conversion Rate are called for pursuant to this Section 10.05, such adjustments shall be made to the Current Market Price as may be necessary or appropriate to effectuate the intent of this Section 10.05 and to avoid unjust or inequitable results as determined in good faith by the Board of Directors.

“Ex” date, when used:

(1) with respect to any issuance or distribution, means the first date on which the shares of Common Stock trade regular way on the relevant exchange or in the relevant market from which the Closing Sale Price was obtained without the right to receive such issuance or distribution;

(2) with respect to any subdivision or combination of shares of Common Stock, means the first date on which the shares of Common Stock trade regular way on such exchange or in such market after the time at which such subdivision or combination becomes effective; and

(3) with respect to any tender or exchange offer, means the first date on which the shares of Common Stock trade regular way on such exchange or in such market after the Expiration Time of such offer.

(ii) “**Fair Market Value**” shall mean the amount which a willing buyer would pay a willing seller in an arm’s-length transaction.

(iii) “**record date**” shall mean, with respect to any dividend, distribution or other transaction or event in which the holders of Common Stock have the right to receive any cash, securities or other property or in which the Common Stock (or other applicable security) is exchanged for or converted into any combination of cash, securities or other property, the date fixed for determination of stockholders entitled to receive such cash, securities or other property (whether such date is fixed by the Board of Directors or by statute, contract or otherwise).

(iv) “**Trading Day**” means a day during which (i) trading in the Common Stock generally occurs, (ii) there is no Market Disruption Event and (iii) a Closing Sale Price for the Common Stock is provided on the Nasdaq Global Market or the Nasdaq Global

Select Market or, if the Common Stock is not listed on the Nasdaq Global Market or the Nasdaq Global Select Market, on the principal other U.S. national or regional securities exchange on which the Common Stock is then listed or, if the Common Stock is not listed on a U.S. national or regional securities exchange, on the principal other market on which the Common Stock is then traded.

(h) The Company may make such increases in the Conversion Rate, in addition to those required by Section 10.05(a)-(f), as the Board of Directors considers to be advisable to avoid or diminish any income tax to holders of Common Stock or rights to purchase Common Stock resulting from any dividend or distribution of stock (or rights to acquire stock) or from any event treated as such for income tax purposes.

To the extent permitted by applicable law and subject to the stockholder approval requirements of the U.S. securities exchange on which the Common Stock is traded, the Company from time to time may increase the Conversion Rate by any amount for any period of time if the period is at least 20 Business Days, the increase is irrevocable during the period and the Board of Directors shall have made a determination that such increase would be in the best interests of the Company, which determination shall be conclusive. Whenever the Conversion Rate is increased pursuant to the preceding sentence, the Company shall mail to Noteholders of record of the Notes a notice of the increase, which notice will be given at least 15 days prior to the effectiveness of any such increase, and such notice shall state the increased Conversion Rate and the period during which it will be in effect.

(i) No adjustment in the Conversion Rate shall be required unless such adjustment would require an increase or decrease of at least one percent (1%) in such rate; provided that any adjustments that by reason of this Section 10.05(i) are not required to be made shall be carried forward and the Company shall make such carry forward adjustments, regardless of whether the aggregate adjustment is less than 1%, (x) annually on the anniversary of the Closing Date and otherwise (y)(1) five Business Days prior to the maturity of the Notes (whether at Stated Maturity or otherwise) or (2) prior to the redemption date or Repurchase Date or Fundamental Change Repurchase Date, unless such adjustment has already been made. All calculations under this Article 10 shall be made by the Company and shall be made to the nearest cent or to the nearest one-ten thousandth (1/10,000) of a share, as the case may be. No adjustment need be made for rights to purchase Common Stock pursuant to a Company plan for reinvestment of dividends or interest or for any issuance of Common Stock or convertible or exchangeable securities or rights to purchase Common Stock or convertible or exchangeable securities. Interest will not accrue on any cash into which the Notes are convertible.

(j) Whenever the Conversion Rate is adjusted as herein provided, the Company will either issue a press release through Business Wire containing the relevant information, file a Current Report on Form 8-K within the time periods prescribed therein disclosing the relevant information or make this information available on the Company’s website or through another public medium as the Company may use at that time. In addition, the Company shall promptly file with the Trustee and any conversion agent other than the Trustee an Officer’s Certificate setting forth the Conversion Rate after such adjustment and setting forth a brief statement of the facts requiring such adjustment. Unless and until a responsible Officer of the Trustee shall have received such Officer’s Certificate, the Trustee shall not be deemed to

have knowledge of any adjustment of the Conversion Rate and may assume that the last Conversion Rate of which it has actual knowledge is still in effect. Promptly after delivery of such certificate, the Company shall prepare a notice of such adjustment of the Conversion Rate setting forth the adjusted Conversion Rate and the date on which each adjustment becomes effective and shall deliver such notice of such adjustment of the Conversion Rate to each Noteholder at his last address appearing on the Register, within 20 calendar days after execution thereof. Failure to deliver such notice shall not affect the legality or validity of any such adjustment.

(k) In any case in which this Section 10.05 provides that an adjustment shall become effective immediately after (1) a record date for an event, (2) the date fixed for the determination of stockholders entitled to receive a dividend or distribution pursuant to Section 10.05(a), (3) a date fixed for the determination of stockholders entitled to receive rights or warrants pursuant to Section 10.05(b), or (4) the Expiration Time for any tender or exchange offer pursuant to Section 10.05(f) (each a “**Determination Date**”), the Company may elect to defer until the occurrence of the applicable Adjustment Event (as hereinafter defined) (x) issuing to any Noteholder converted after such Determination Date and before the occurrence of such Adjustment Event, the Additional Shares of Common Stock, if any, or other securities issuable upon such conversion by reason of the adjustment required by such Adjustment Event over and above the Common Stock, if any, issuable upon such conversion before giving effect to such adjustment and (y) paying to such Noteholder any amount in cash in lieu of any fractional share pursuant to Section 10.03. For purposes of this Section 10.05(j), the term “**Adjustment Event**” shall mean:

- (i) in any case referred to in clause (1) hereof, the occurrence of such event,
- (ii) in any case referred to in clause (2) hereof, the date any such dividend or distribution is paid or made,
- (iii) in any case referred to in clause (3) hereof, the date of expiration of such rights or warrants, and
- (iv) in any case referred to in clause (4) hereof, the date a sale or exchange of Common Stock pursuant to such tender or exchange offer is consummated and becomes irrevocable.

(l) For purposes of this Section 10.05, the number of shares of Common Stock at any time outstanding shall not include shares held in the treasury of the Company but shall include shares issuable in respect of scrip certificates issued in lieu of fractions of shares of Common Stock. The Company will not pay any dividend or make any distribution on shares of Common Stock held in the treasury of the Company.

(m) No adjustment to the Conversion Rate shall be made pursuant to this Section 10.05 if the Noteholders may participate in the transaction that would otherwise give rise to adjustment pursuant to this Section 10.05.

SECTION 10.06. Effect of Reclassification, Consolidation, Merger or Sale. If any of the following events occur, namely:

- (a) any reclassification or change of the outstanding Common Stock (other than a change in par value, or from par value to no par value, or from no par value to par value, or as a result of a subdivision or combination),
- (b) any consolidation or merger of the Company with or into another Person, or
- (c) any sale, lease, transfer, conveyance or other disposition of all or substantially all of the Company’s assets and those of its Subsidiaries taken as a whole to any other Person or Persons, as a result of which holders of Common Stock shall be entitled to receive stock, other securities or other property or assets (including cash or any combination thereof) with respect to or in exchange for such Common Stock,

in each case, the Company or the successor or purchasing corporation, as the case may be, shall execute with the Trustee a supplemental indenture (which shall comply with the Trust Indenture Act as in force at the date of execution of such supplemental indenture, if such supplemental indenture is then required to so comply) providing that such Notes shall, without the consent of any Noteholders, be convertible into the kind and amount of shares of stock and other securities or property or assets (including cash or any combination thereof) (the “**Applicable Consideration**”) that such Noteholder would have been entitled to receive upon such reclassification, change, consolidation, merger, sale, lease, transfer, conveyance or other disposition had such Notes been converted into Common Stock immediately prior to such reclassification, change, consolidation, merger, sale, lease, transfer, conveyance or other disposition; provided that in the event holders of Common Stock have the opportunity to elect the form of consideration to be received in the event of such reclassification, change, consolidation, merger, sale, lease, transfer, conveyance or other disposition, then from and after the effective date of such transaction, the Notes shall be convertible into the consideration that a majority of the holders of Common Stock who made such an election received in such transaction and the term “**Applicable Consideration**” shall be construed accordingly. Such supplemental indenture shall provide for adjustments that shall be as nearly equivalent as may be practicable to the adjustments provided for in this Article 10. If, in the case of any such reclassification, change, consolidation, merger, sale, lease, transfer, conveyance or other disposition, the stock or other securities and assets receivable thereupon by a holder of Common Stock includes shares of stock or other securities and assets of a corporation other than the successor or purchasing corporation, as the case may be, in such reclassification, change, consolidation, merger, sale, lease, transfer, conveyance or other disposition, then such supplemental indenture shall also be executed by such other corporation and shall contain such additional provisions to protect the interests of the Noteholders as the Board of Directors shall reasonably consider necessary by reason of the foregoing, including to the extent practicable the provisions providing for the conversion rights set forth in this Article 10.

The Company shall cause notice of the execution of such supplemental indenture to be delivered to each Noteholder, at the address of such Noteholder as it appears on the register of

the Notes maintained by the Registrar, within 20 days after execution thereof. Failure to deliver such notice shall not affect the legality or validity of such supplemental indenture.

The above provisions of this Section 10.06 shall similarly apply to successive reclassifications, changes, consolidations, mergers, sales, leases, transfers, conveyances or other dispositions.

If this Section 10.06 applies to any event or occurrence, Section 10.05 shall not apply. Notwithstanding this Section 10.06, if a Public Acquirer Change of Control occurs and the Company elects to adjust its Conversion Obligation and the Conversion Rate pursuant to Section 10.13, the provisions of Section 10.13 shall apply to the conversion instead of this Section 10.06.

In the event that the Company has made an irrevocable election to make a cash payment of Principal upon conversion pursuant to Section 10.14 hereof, such election shall remain binding notwithstanding the form of Applicable Consideration paid to holders of Common Stock.

Any Additional Shares that a Noteholder is entitled to receive upon conversion pursuant to Section 10.04(b), if applicable, shall not be payable in shares of Common Stock, but shall represent a right to receive the aggregate amount of cash, securities or other property into which the Additional Shares would convert as a result of such recapitalization, change, consolidation, merger, sale, lease, transfer, conveyance or other disposition.

SECTION 10.07. Taxes on Shares Issued. The issue of stock certificates on conversions of Notes shall be made without charge to the converting Noteholder for any documentary, stamp or similar issue or transfer tax in respect of the issue thereof. The Company shall not, however, be required to pay any such tax which may be payable in respect of any transfer involved in the issue and delivery of stock in any name other than that of the holder of any Notes converted, and the Company shall not be required to issue or deliver any such stock certificate unless and until the Person or Persons requesting the issue thereof shall have paid to the Company the amount of such tax or shall have established to the satisfaction of the Company that such tax has been paid.

SECTION 10.08. Reservation of Shares, Shares to be Fully Paid; Compliance with Governmental Requirements; Listing of Common Stock. The Company shall provide, free from preemptive rights, out of its authorized but unissued shares or shares held in treasury, sufficient shares of Common Stock to provide for the conversion of the Notes, including any Additional Shares, from time to time as such Notes are presented for conversion.

Before taking any action which would cause an adjustment increasing the Conversion Rate to an amount that would cause the Conversion Price to be reduced below the then par value, if any, of the shares of Common Stock issuable upon conversion of the Notes, the Company will take all corporate action which may, in the opinion of its counsel, be necessary in order that the Company may validly and legally issue shares of such Common Stock at such adjusted Conversion Rate.

The Company covenants that all shares of Common Stock which may be issued upon conversion of Notes will upon issue be fully paid and non-assessable by the Company and free from all taxes, liens and charges with respect to the issue thereof.

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The Company covenants that, if any shares of Common Stock to be provided for the purpose of conversion of Notes hereunder require registration with or approval of any governmental authority under any federal or state law before such shares may be validly issued upon conversion, the Company will in good faith and as expeditiously as possible, to the extent then permitted by the rules and interpretations of the Commission (or any successor thereto), endeavor to secure such registration or approval, as the case may be.

The Company further covenants that, if at any time the Common Stock shall be listed on The New York Stock Exchange, the Nasdaq Global Market or any other national securities exchange or automated quotation system, the Company will, if permitted by the rules of such exchange or automated quotation system, list and keep listed, so long as the Common Stock shall be so listed on such exchange or automated quotation system, all Common Stock issuable upon conversion of the Notes; provided that if the rules of such exchange or automated quotation system permit the Company to defer the listing of such Common Stock until the first conversion of the Notes into Common Stock in accordance with the provisions of this Indenture, the Company covenants to list such Common Stock issuable upon conversion of the Notes in accordance with the requirements of such exchange or automated quotation system at such time.

SECTION 10.09. Responsibility of Trustee. The Trustee and any other conversion agent shall not at any time be under any duty or responsibility to any Noteholder to determine the Conversion Rate or whether any facts exist which may require any adjustment of the Conversion Rate, or with respect to the nature or extent or calculation of any such adjustment when made, or with respect to the method employed, or herein or in any supplemental indenture provided to be employed, in making the same. The Trustee and any other conversion agent shall not be accountable with respect to the validity or value (or the kind or amount) of any shares of Common Stock, or of any capital stock, other securities or other assets or property, which may at any time be issued or delivered upon the conversion of any Notes; and the Trustee and any other conversion agent make no representations with respect thereto. Neither the Trustee nor any conversion agent shall be responsible for any failure of the Company to issue, transfer or deliver any shares of Common Stock or stock certificates or other securities or property or cash upon the surrender of any Notes for the purpose of conversion or to comply with any of the duties, responsibilities or covenants of the Company contained in this Article 10. Without limiting the generality of the foregoing, neither the Trustee nor any conversion agent shall be under any responsibility to determine the correctness of any provisions contained in any supplemental indenture entered into pursuant to Section 10.06 relating either to the kind or amount of shares of capital stock or other securities or other assets or property (including cash) receivable by Noteholders upon the conversion of their Notes after any event referred to in such Section 10.06 or to any adjustment to be made with respect thereto, but, subject to the provisions of Section 9.01, may accept as conclusive evidence of the correctness of any such provisions, and shall be protected in relying upon, the Officer's Certificate (which the Company shall be obligated to file with the Trustee prior to the execution of any such supplemental indenture) with respect thereto.

SECTION 10.10. Notice to Holders Prior to Certain Actions. In case:

(a) the Company shall declare a dividend (or any other distribution) on its Common Stock that would require an adjustment in the Conversion Rate pursuant to Section 10.05; or

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(b) the Company shall authorize the granting to the holders of all of its Common Stock rights or warrants to subscribe for or purchase any share of any class or any other rights or warrants; or

(c) of any reclassification or reorganization of the Common Stock of the Company (other than a subdivision or combination of its outstanding Common Stock, or a change in par value, or from par value to no par value, or from no par value to par value), or of any consolidation or merger to which the Company is a party and for which approval of any stockholders of the Company is required, or of the sale or transfer of all or substantially all of the assets of the Company; or

(d) of the voluntary or involuntary dissolution, liquidation or winding up of the Company;

the Company shall cause to be filed with the Trustee and to be delivered to each Noteholder at its address appearing on the Register provided for in Section 2.05 of this Indenture, a notice stating (x) the date on which a record is to be taken for the purpose of such dividend, distribution or rights or warrants, or, if a record is not to be taken, the date as of which the holders of Common Stock of record to be entitled to such dividend, distribution or rights are to be determined, or (y) the date on which such reclassification, consolidation, merger, sale, transfer, dissolution, liquidation or winding up is expected to become effective or occur, and the date as of which it is expected that holders of Common Stock of record shall be entitled to exchange their Common Stock for securities or other property deliverable upon such reclassification, consolidation, merger, sale, transfer, dissolution, liquidation or winding up. Failure to give such notice, or any defect therein, shall not affect the legality or validity of such dividend, distribution, reclassification, consolidation, merger, sale, transfer, dissolution, liquidation or winding up.

SECTION 10.11. Stockholder Rights Plans. If the rights provided for in any existing or future rights plan adopted by the Company have separated from the shares of Common Stock in accordance with the provisions of the applicable stockholder rights agreement so that the Noteholders would not be entitled to receive any rights in respect of Common Stock issuable upon conversion of the Notes, the Conversion Rate will be adjusted as provided in Section 10.05(d). If such rights have not separated, any shares of Common Stock delivered upon the conversion of Notes shall be accompanied by such rights.

SECTION 10.12. Settlement Upon Conversion. (a) Except to the extent the Company has irrevocably elected to make cash payment of Principal upon conversion pursuant to Section 10.14, the Company may elect to deliver either shares of Common Stock, cash or a combination of cash and shares of Common Stock in satisfaction of its obligations upon conversion of the Notes (including with respect to Additional Shares).

(b) Except to the extent the Company has irrevocably elected to make cash payment of Principal upon conversion pursuant to Section 10.14, the Company shall inform the Noteholders of its method of settlement upon conversion by giving notice of such method to the Trustee:

(i) if the Company has called the Notes for redemption, in its redemption notice;

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(ii) if a Fundamental Change has occurred, in the Company Repurchase Notice;

(iii) in respect of Notes to be converted during the period beginning 25 Trading Days preceding the Maturity Date and ending one Trading Day preceding the Maturity Date, 26 Trading Days preceding the Maturity Date; and

(iv) in all other cases, no later than two Trading Days following the Conversion Date;

provided that, if the Company has not irrevocably elected to make a cash payment of Principal upon conversion pursuant to Section 10.14 or otherwise given notice of its intention to deliver cash or a combination of cash and shares of Common Stock upon settlement, the Company will deliver only Common Stock in satisfaction of its obligations upon conversion of the Notes.

(c) If the Company chooses to satisfy all or any portion of the conversion obligation in cash, the Company will notify the converting Holder through the Trustee of the dollar amount to be satisfied in cash, which must be expressed either as a percentage of the conversion obligation or as the lesser of (x) a fixed dollar amount and (y) the Conversion Value. The Company will treat all Noteholders converting on the same Trading Day in the same manner with respect to settlement of conversion of the Notes; provided that, the Company will not have any obligation to satisfy its conversion obligations arising on different Trading Days in the same manner except to the extent it has made an irrevocable election to make cash payment of Principal upon conversion pursuant to Section 10.14.

(d) If the Company timely elects to satisfy all or any portion of the Conversion Obligation in cash, the Conversion Notice may be retracted by the converting Holder at any time during the Conversion Retraction Period; provided that, no Noteholder may retract its Conversion Notice if (i) the Company irrevocably elected to make a cash payment of Principal upon conversion, (ii) the Noteholder is converting its Note in connection with a redemption or a Fundamental Change, (iii) the Noteholder is converting its Note during the period beginning 25 Trading Days preceding the Maturity Date and ending one Trading Day preceding the Maturity Date or (iv) the Company does not elect to satisfy any portion of its conversion obligation in cash.

(e) If the Conversion Notice has not been retracted, then (i) settlement in shares of Common Stock only will occur as soon as practicable after the Company notifies Noteholders that it has chosen this method of settlement, but in no event later than three Trading Days thereafter (ii) settlement in cash and/or shares of Common Stock will occur on the second Trading Day following the final day of the Conversion Period.

(f) If the Company elects to satisfy the entire conversion obligation in shares of Common Stock, the Company will deliver to Holders surrendering Notes for conversion a number of shares of Common Stock equal to (A) the Principal to be converted divided by \$1,000 multiplied by (B) the then-effective Conversion Rate.

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(g) If the Company elects to satisfy the entire conversion obligation in cash, the Company will deliver to Holders surrendering Notes for conversion, for each \$1,000 Principal amount of Notes converted, cash in an amount equal to the Conversion Value.

(h) If the Company elects to satisfy the conversion obligation in a combination of cash and shares of Common Stock, the Company will deliver to Holders surrendering Notes for conversion, for each \$1,000 Principal amount of Notes converted:

(i) (x) the fixed dollar amount per \$1,000 principal amount of the Notes of the conversion obligation to be satisfied in cash specified in the notice regarding the Company's chosen method of settlement or, if lower, the Conversion Value in cash, or (y) the percentage of the conversion obligation to be satisfied in cash specified in the notice regarding the Company's chosen method of settlement multiplied by the Conversion Value, as the case may be (the "Cash Amount"); and

(ii) a number of shares of Common Stock for each of the 20 Trading Days in the Conversion Period equal to 1/20th of (i) the Conversion Rate then in effect minus (ii) the quotient of (x) the Cash Amount divided by (y) the Closing Sale Price of Common Stock for that Trading Day (plus cash in lieu of fractional shares if applicable).

For purposes of this Section 10.12,

"Conversion Value," for every \$1,000 principal amount of the Notes being converted, means an amount equal to the sum of the Daily Conversion Values for each of the 20 Trading Days in the Conversion Period.

"Daily Conversion Value" for any Trading Day equals 1/20th of the product of (a) the Conversion Rate in effect on that day and (b) the Closing Sale Price of the Common Stock on that day.

SECTION 10.13. Conversion After a Public Acquirer Change of Control.

(a) In the event of a Public Acquirer Change of Control, the Company may, in lieu of adjusting the Conversion Rate pursuant to Section 10.04(b), elect to adjust its conversion obligation and the Conversion Rate such that from and after the Effective Date of such Public Acquirer Change of Control, Noteholders shall be entitled to convert their Notes, in accordance with Section 10.02 hereof, into shares of Public Acquirer Common Stock and the Conversion Rate in effect immediately before the Public Acquirer Change of Control shall be adjusted by multiplying it by a fraction:

(1) the numerator of which shall be (A) in the case of a Public Acquirer Change of Control, pursuant to which the Common Stock is converted solely into cash, the value of such cash payable per share of Common Stock or (B) in the case of any other Public Acquirer Change of Control, the average of the Closing Sale Prices of the

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Common Stock for the five consecutive Trading Days prior to but excluding the Effective Date of such Public Acquirer Change of Control; and

(2) the denominator of which shall be the average of the Closing Sale Prices of the Public Acquirer Common Stock for the five consecutive Trading Days commencing on the Trading Day next succeeding the Effective Date of such Public Acquirer Change of Control.

(b) The Company shall notify Noteholders of its election by providing notice as set forth in Section 10.04(b).

(c) If the Company elects to make the adjustment to the Conversion Rate described in Section 10.13(a) in the event of a Public Acquirer Change of Control, Noteholders will not be entitled to receive any Additional Shares pursuant to Section 10.04(b). In addition, following such an election, the provisions herein shall continue to apply except that references to "Common Stock" shall be deemed to refer to Public Acquirer Common Stock.

SECTION 10.14. Irrevocable Election of Cash Payment Upon Conversion.

At any time on or prior to the 26th Trading Day preceding the Maturity Date, the Company may irrevocably elect to satisfy in cash its conversion obligation with respect to, the lower of (i) the Conversion Value or (ii) the Principal amount of the Notes to be converted after the date of such election, with any remaining amount to be satisfied in shares of the Common Stock or cash as the Company may subsequently elect. Such irrevocable election with respect to the Principal amount of the Notes would be in the Company's sole discretion without the consent of the Noteholders. If the Company makes such election, the Company will notify the Trustee and the Noteholders at their addresses shown in the Register of the Registrar.

ARTICLE 11

RESERVED

ARTICLE 12

SUBORDINATION

SECTION 12.01. Agreement to Subordinate. The Company covenants and agrees, and each Noteholder by accepting a Note likewise covenants and agrees, that the payment of Principal and interest (including Special Interest and Additional Interest, if any) with respect to the Notes shall be subordinated in right of payment, to the extent and in the manner provided in this Article 12, to the prior payment in full in cash or Cash Equivalents of all Senior Indebtedness and that the subordination is for the benefit of and enforceable by the holders of such Senior Indebtedness.

SECTION 12.02. Liquidation, Dissolution, Bankruptcy. Upon any payment or distribution of the assets of the Company to creditors upon a liquidation, winding up or

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dissolution of the Company or in a bankruptcy, reorganization, insolvency, receivership or similar proceeding relating to the Company or its properties:

(a) holders of Senior Indebtedness shall be entitled to receive payment in full in cash or Cash Equivalents of such Senior Indebtedness before the Noteholders shall be entitled to receive any payment from the Company of amounts due with respect to the Notes; and

(b) until the Senior Indebtedness is paid in full in cash or Cash Equivalents, any payment or distribution to which Noteholders would be entitled but for this Article 12 shall be made to holders of such Senior Indebtedness as their interests may appear.

SECTION 12.03. Payments to Noteholders. No payment shall be made with respect to the Principal of, premium, if any, or interest, on the Notes, (including but not limited to, Additional Interest, if any, and the redemption price with respect to the Notes called or submitted for redemption in accordance with this Indenture), if:

(a) a default in the payment of Principal, premium, if any, interest, rent or other obligations in respect of Senior Indebtedness occurs and is continuing beyond any applicable period of grace or upon the acceleration of the maturity thereof (a “**Payment Default**”); or

(b) a default, other than a Payment Default, on any Designated Senior Indebtedness occurs and is continuing that then permits holders of such Designated Senior Indebtedness to accelerate its maturity and the Trustee receives a notice of the default (a “**Payment Blockage Notice**”) from a holder of Designated Senior Indebtedness, a Representative of Designated Senior Indebtedness or the Company (a “**Non-Payment Default**”).

If the Trustee receives any Payment Blockage Notice pursuant to clause (b) above, no subsequent Payment Blockage Notice shall be effective for purposes of this Section 12.03 unless and until (A) at least 365 days shall have elapsed since the initial effectiveness of the immediately prior Payment Blockage Notice and (b) all scheduled payments of Principal, premium, if any, and interest, if any, on the Notes that have come due have been paid in full in cash or Cash Equivalents. No Non-Payment Default that existed or was continuing on the date of delivery of any Payment Blockage Notice to the Trustee shall be, or be made, the basis for a subsequent Payment Blockage Notice.

The Company may and shall resume payments on and distributions in respect of the Notes upon:

(1) in the case of a Payment Default, the date upon which any such Payment Default is cured or waived or ceases to exist, or

(2) in the case of a Non-Payment Default, the earlier of (a) the date upon which such default is cured or waived or ceases to exist or (b) 179 days after the applicable Payment Blockage Notice is received by the Trustee (the “**Payment Blockage Period**”), unless this Article 12 otherwise prohibits the payment or distribution at the time of such payment or distribution.

Regardless of anything to the contrary herein, nothing shall prevent (a) any payment by the Trustee to the Noteholders of amounts deposited with it pursuant to Article 8 or (b) any payment by the Trustee or the paying Agent as permitted by Section 12.09.

SECTION 12.04. Acceleration of Securities. If payment of the Notes is accelerated because of an Event of Default and a demand for payment is made on the Company, pursuant to the directions of the Representative and the Company, the Trustee shall promptly notify the holders of the Senior Indebtedness (or the Representative of such holders) of such demand. If any Senior Indebtedness is outstanding, the Company may not make payments of amounts due with respect to the Notes until five Business Days after such holders or the Representative of the holders of the Designated Senior Indebtedness receive notice of such demand and, thereafter, may make payments of amounts due with respect to the Notes.

SECTION 12.05. When Distribution Must Be Paid Over. In the event the Company shall make any payment or distribution to the Trustee with respect to the Notes at a time when such payment or distribution of the Company’s assets of any kind, whether in cash, property or securities, including, without limitation, by way of set-off or otherwise is prohibited by Section 12.02 or 12.03, such payment shall be held by the Trustee, in trust for the benefit of, and shall be paid forthwith over and delivered to, pursuant to the directions of the Representative and the Company, the holders of Senior Indebtedness (pro rata as to each of such holders on the basis of the respective amounts of Senior Indebtedness held by them) or their Representative, as their respective interests may appear, for application to the payment of all Senior Indebtedness remaining unpaid to the extent necessary to pay all Senior Indebtedness in full in cash or payment satisfactory to the holders of Senior Indebtedness of all Senior Indebtedness remaining unpaid in accordance with its terms, after giving effect to any concurrent payment or distribution to or for the holders of Senior Indebtedness. If a payment or distribution is made to Noteholders that because of this Article 12 should not have been made to them, the Noteholders who receive the payment or distribution shall hold such payment or distribution in trust for holders of the Senior Indebtedness and pay it over to them as their respective interests may appear.

SECTION 12.06. Subrogation. After all Senior Indebtedness is paid in full and until the Notes are paid in full, Noteholders shall be subrogated to the rights of holders of such Senior Indebtedness to receive distributions applicable to Senior Indebtedness. A distribution made under this Article 12 to holders of Senior Indebtedness which otherwise would have been made to Noteholders is not, as between the Company and Noteholders, a payment by the Company on such Senior Indebtedness.

SECTION 12.07. Relative Rights. This Article 12 defines the relative rights of Noteholders and holders of Senior Indebtedness. Nothing in this Indenture shall:

(a) impair, as between the Company and Noteholders, the obligation of the Company which is absolute and unconditional, to make payments with respect to the Notes;

(b) affect the relative rights of Noteholders and creditors of the Company other than holders of Senior Indebtedness; or

(c) prevent the Trustee or any Noteholder from exercising its available remedies upon a Default by the Company under its obligations with respect to the Notes, subject to the rights of holders of Senior Indebtedness to receive distributions otherwise payable to Noteholders.

SECTION 12.08. Subordination May Not Be Impaired. No right of any holder of Senior Indebtedness to enforce the subordination of the obligations of the Company hereunder shall be impaired by any act or failure to act by the Company or by its failure to comply with this Indenture.

SECTION 12.09. Rights of Trustee and Paying Agent. Notwithstanding Section 12.03, the Trustee or the Paying Agent may continue to make payments on the Notes and shall not be charged with knowledge of the existence of facts that would prohibit the making of any such payments unless, not less than three Business Days prior to the date of such payment, a Trust Officer of the Trustee receives written notice satisfactory to it that payments may not be made under this Article 12. The Company, the Registrar or co-registrar, the Paying Agent, a Representative or a holder of Senior Indebtedness may give the notice; provided, however, that if an issue of Senior Indebtedness has a Representative, only the Representative may give the notice.

The Trustee in its individual or any other capacity may hold Senior Indebtedness with the same rights it would have if it were not Trustee. The Registrar and co-registrar and the Paying Agent may do the same with like rights. The Trustee shall be entitled to all the rights set forth in this Article 12 with respect to any Senior Indebtedness which may at any time be held by it, to the same extent as any other holder of Senior Indebtedness; and nothing in Article 7 shall deprive the Trustee of any of its rights as such holder. Nothing in this Article 12 shall apply to claims of, or payments to, the Trustee under or pursuant to Section 7.07.

SECTION 12.10. Distribution or Notice to Representative. Whenever a distribution is to be made or a notice given to holders of Senior Indebtedness, the distribution may be made and the notice given to their Representative (if any).

SECTION 12.11. Article 12 Not to Prevent Events of Default or Limit Right to Accelerate. The failure of the Company to make a payment on any of its obligations, including with respect to the Notes, by reason of any provision in this Article 12 shall not be construed as preventing the occurrence of a Default by the Company under such obligations, including with respect to the Notes. Nothing in this Article 12 shall have any effect on the right of the Noteholders or the Trustee to make a demand for payment on the Company pursuant to the terms of the Notes.

SECTION 12.12. Trustee Entitled to Rely. Upon any payment or distribution pursuant to this Article 12, the Trustee and the Noteholders shall be entitled to rely (i) upon any order or decree of a court of competent jurisdiction in which any proceedings of the nature referred to in Section 12.02 are pending, (ii) upon a certificate of the liquidating trustee or agent or other Person making such payment or distribution to the Trustee or to the Noteholders or (iii) upon the Representatives for the holders of Senior Indebtedness for the purpose of ascertaining the Persons entitled to participate in such payment or distribution, the holders of such Senior

Indebtedness and other Indebtedness, the amount thereof or payable thereon, the amount or amounts paid or distributed thereon and all other facts pertinent thereto or to this Article 12. In the event that the Trustee determines, in good faith, that evidence is required with respect to the right of any Person as a holder of Senior Indebtedness to participate in any payment or distribution pursuant to this Article 12, the Trustee may request such Person to furnish evidence to the reasonable satisfaction of the Trustee as to the amount of such Senior Indebtedness held by such Person, the extent to which such Person is entitled to participate in such payment or distribution and other facts pertinent to the rights of such Person under this Article 12, and, if such evidence is not furnished, the Trustee may defer any payment to such Person pending judicial determination as to the right of such Person to receive such payment. The provisions of Sections 7.01 and 7.02 shall be applicable to all actions or omissions of actions by the Trustee pursuant to this Article 12.

SECTION 12.13. Trustee to Effectuate Subordination. Each Noteholder by accepting a Note authorizes and directs the Trustee on his or her behalf to take such action as may be necessary or appropriate to acknowledge or effectuate the subordination between the Noteholders and the holders of Senior Indebtedness as provided in this Article 12 and appoints the Trustee as attorney-in-fact for any and all such purposes.

SECTION 12.14. Trustee Not Fiduciary for Holders of Senior Indebtedness. The Trustee shall not be deemed to owe any fiduciary duty to the holders of Senior Indebtedness and shall not be liable to any such holders if it shall mistakenly pay over or distribute to Noteholders or the Company or any other Person, money or assets to which any holders of Senior Indebtedness shall be entitled by virtue of this Article 12 or otherwise.

SECTION 12.15. Reliance by Holders of Senior Indebtedness on Subordination Provisions. Each Noteholder by accepting a Note acknowledges and agrees that the foregoing subordination provisions are, and are intended to be, an inducement and a consideration to each holder of any Senior Indebtedness, whether such Senior Indebtedness was created or acquired before or after the issuance of the Notes, to acquire and continue to hold, or to continue to hold, such Senior Indebtedness and such holder of Senior Indebtedness (including, without limitation, Designated Senior Indebtedness) shall be deemed conclusively to have relied on such subordination provisions in acquiring and continuing to hold, or in continuing to hold, such Senior Indebtedness.

SECTION 12.16. Obligation of Company Unconditional. Nothing contained in this Article 12 or elsewhere in this Indenture or in any Note is intended to or shall impair, as between the Company, its creditors other than holders of Senior Indebtedness and the Noteholders, the obligation of the Company, which is absolute and unconditional, to pay to the Noteholders all amounts due with respect to the Notes as and when the same shall become due and payable in accordance with their terms, or is intended to or shall affect the relative rights of the Noteholders and creditors of the Company, other than the holders of the Senior Indebtedness, nor shall anything herein or therein prevent the Trustee or the Holder of any Note from exercising all remedies otherwise permitted by applicable law upon Default under this Indenture, subject to the rights, if any, under this Article 12 of the holders of Senior Indebtedness in respect of cash, property or securities of the Company received upon the exercise of any such remedy. Upon any distribution of assets of the Company referred to in this Article 12, the Trustee, subject to the

provisions of Sections 7.01 and 7.02, and the Noteholders shall be entitled to rely upon any order or decree by any court of competent jurisdiction in which such dissolution, winding up, liquidation or reorganization proceedings are pending, or a certificate of the liquidating trustee or agent or other person making any distribution to the Trustee or the Noteholders, for the purpose of ascertaining the persons entitled to participate in such distribution, the holders of the Senior Indebtedness and other Indebtedness of the Company, the amount thereof or payable thereon, the amount or amounts paid or distributed thereon and all other facts pertinent thereto or to this Article 12. Nothing contained in this Article 12 or elsewhere in this Indenture or in any Note is intended to or shall affect the obligation of the Company to make, or prevent the Company from making, at any time except during the pendency of any dissolution, winding up, liquidation or reorganization proceeding, and except during the continuance of any default specified in Section 12.03 (not cured or waived), payments at any time of all amounts due with respect to the Notes.

SECTION 12.17. Not to Prevent Events of Default. The failure to make any payment due with respect to the Notes by reason of any provision of this Article 12 shall not be construed as preventing the occurrence of an Event of Default under Section 6.01.

ARTICLE 13

MISCELLANEOUS

SECTION 13.01. Trust Indenture Act Controls. If any provision of this Indenture limits, qualifies or conflicts with another provision which is required to be included in this Indenture by the TIA, the required provision shall control.

SECTION 13.02. Notices. Any notice or communication shall be in writing and delivered in person, or mailed by first-class mail addressed as follows:

if to the Company:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attention: Lynne Parshall, Senior Vice President and Chief Financial Officer

if to the Trustee:

Wells Fargo Bank, N.A.
Corporate Trust Services
608 2nd Avenue South
MAC N9303-120
Minneapolis, MN 55479
Attention: Isis Pharmaceuticals Account Manager

The Company or the Trustee by notice to the other may designate additional or different addresses for subsequent notices or communications.

Any notice or communication delivered to a Noteholder shall be delivered to the Noteholder at the Noteholder's address as it appears on the Register of the Registrar and shall be sufficiently given if so delivered within the time prescribed.

Failure to deliver a notice or communication to a Noteholder or any defect in it shall not affect its sufficiency with respect to other Noteholders. If a notice or communication is delivered in the manner provided above, it is duly given, whether or not the addressee receives it.

SECTION 13.03. Communication by Noteholders with Other Noteholders. Noteholders may communicate pursuant to TIA § 312(b) with other Noteholders with respect to their rights under this Indenture or the Notes. The Company, the Trustee, the Registrar and anyone else shall have the protection of TIA § 312(c).

SECTION 13.04. Certificate and Opinion as to Conditions Precedent. Upon any request or application by the Company to the Trustee to take or refrain from taking any action under this Indenture, the Company shall furnish to the Trustee upon request:

- (a) an Officer's Certificate in form and substance reasonably satisfactory to the Trustee stating that, in the opinion of the signers, all conditions precedent, if any, provided for in this Indenture relating to the proposed action have been complied with; and/or
- (b) an Opinion of Counsel in form and substance reasonably satisfactory to the Trustee stating that, in the opinion of such counsel, all such conditions precedent have been complied with.

Each signer of an Officer's Certificate or an Opinion of Counsel may (if so stated) rely, effectively, upon an Opinion of Counsel as to matters and an Officer's Certificate as to factual matters if such register reasonably and in good faith believes in the accuracy of the document relied upon.

SECTION 13.05. Statements Required in Certificate or Opinion. Each Officer's Certificate or Opinion of Counsel requested by the Trustee with respect to compliance with a covenant or condition provided for in this Indenture shall include:

- (a) a statement that the individual making such certificate or opinion has read such covenant or condition;
- (b) a brief statement as to the nature and scope of the examination or investigation upon which the statements or opinions contained in such certificate or opinion are based;

(c) a statement that, in the opinion of such individual, he or she has made such examination or investigation as is necessary to enable him to express an informed opinion as to whether or not such covenant or condition has been complied with; and

(d) a statement as to whether or not, in the opinion of such individual, such covenant or condition has been complied with.

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SECTION 13.06. When Notes Disregarded. In determining whether the Noteholders of the required principal amount of Notes have concurred in any direction, waiver or consent, Notes owned by the Company or by any Person directly or indirectly controlling or controlled by or under direct or indirect common control with the Company shall be disregarded and deemed not to be outstanding, except that, for the purpose of determining whether the Trustee shall be protected in relying on any such direction, waiver or consent, only Notes which a Trust Officer of the Trustee knows are so owned shall be so disregarded. Subject to the foregoing, only Notes outstanding at the time shall be considered in any such determination.

SECTION 13.07. Rules by Trustee, Paying Agent and Registrar. The Trustee may make reasonable rules for action by or a meeting of Noteholders. The Registrar and the Paying Agent may make reasonable rules for their functions.

SECTION 13.08. Legal Holidays. A “**Legal Holiday**” is a Saturday, a Sunday or a day on which banking institutions are not required to be open in the City of New York, in the State of New York or in the city in which the Trustee administers its Corporate Trust Office. If a payment date is a Legal Holiday, payment shall be made on the next succeeding day that is not a Legal Holiday, and no interest shall accrue for the intervening period. If a regular record date is a Legal Holiday, the record date shall not be affected.

SECTION 13.09. GOVERNING LAW. THIS INDENTURE AND THE NOTES SHALL BE GOVERNED BY, AND CONSTRUED IN ACCORDANCE WITH, THE LAWS OF THE STATE OF NEW YORK.

SECTION 13.10. No Recourse Against Others. A director, officer, employee or stockholder, as such, of the Company shall not have any liability for any obligations of the Company under the Notes or this Indenture or for any claim based on, in respect of or by reason of such obligations or their creation. By accepting a Note, each Noteholder shall waive and release all such liability. The waiver and release shall be part of the consideration for the issue of the Notes.

SECTION 13.11. Successors. All agreements of the Company in this Indenture and the Notes shall bind its successors. All agreements of the Trustee in this Indenture shall bind its successors.

SECTION 13.12. Multiple Originals. The parties may sign any number of copies of this Indenture. Each signed copy shall be an original, but all of them together represent the same agreement. One signed copy is enough to prove this Indenture.

SECTION 13.13. Table of Contents; Headings. The table of contents, cross-reference sheet and headings of the Articles and Sections of this Indenture have been inserted for convenience of reference only, are not intended to be considered a part hereof and shall not modify or restrict any of the terms or provisions hereof.

SECTION 13.14. Severability. In case any provision in this Indenture or in the Notes shall be invalid, illegal or unenforceable, then (to the extent permitted by law) the validity, legality and enforceability of the remaining provisions shall not in any way be affected or impaired thereby.

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SECTION 13.15. Indenture, Notes and Guarantee Solely Corporate Obligations. No recourse for the payment of the Principal of or, premium, if any, or interest on any Notes, or under any Guarantee, or for any claim based upon any Notes or Guarantee or otherwise in respect thereof, and no recourse under or upon any obligation, covenant or agreement of the Company in this Indenture or in any supplemental indenture or in any Notes or Guarantee, or because of the creation of any indebtedness represented thereby, shall be had against any incorporator, stockholder, member, manager, employee, agent, officer, director or subsidiary, as such, past, present or future, of the Company or any of the Company’s subsidiaries or of any successor thereto, either directly or through the Company or any of the Company’s subsidiaries or any successor thereto, whether by virtue of any constitution, statute or rule of law, or by the enforcement of any assessment or penalty or otherwise; it being expressly understood that all such liability is hereby expressly waived and released as a condition of, and as a consideration for, the execution of this Indenture and the issue of the Notes.

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IN WITNESS WHEREOF, the parties have caused this Indenture to be duly executed as of the date first written above.

ISIS PHARMACEUTICALS, INC., as Issuer

by /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Executive Vice President and Chief
Financial Officer

WELLS FARGO BANK, N.A., as Trustee,

by /s/ Lynn M. Steiner
Name: Lynn M. Steiner
Title: Vice President

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EXHIBIT A

[FORM OF FACE OF NOTE]

[Global Notes Legend]

UNLESS THIS CERTIFICATE IS PRESENTED BY AN AUTHORIZED REPRESENTATIVE OF THE DEPOSITORY TRUST COMPANY, A NEW YORK CORPORATION ("DTC"), NEW YORK, NEW YORK, TO THE COMPANY OR ITS AGENT FOR REGISTRATION OF TRANSFER, EXCHANGE OR PAYMENT, AND ANY CERTIFICATE ISSUED IS REGISTERED IN THE NAME OF CEDE & CO. OR SUCH OTHER NAME AS IS REQUESTED BY AN AUTHORIZED REPRESENTATIVE OF DTC (AND ANY PAYMENT IS MADE TO CEDE & CO., OR TO SUCH OTHER ENTITY AS IS REQUESTED BY AN AUTHORIZED REPRESENTATIVE OF DTC), ANY TRANSFER, PLEDGE OR OTHER USE HEREOF FOR VALUE OR OTHERWISE BY OR TO ANY PERSON IS WRONGFUL INASMUCH AS THE REGISTERED OWNER HEREOF, CEDE & CO., HAS AN INTEREST HEREIN.

TRANSFERS OF THIS GLOBAL SECURITY SHALL BE LIMITED TO TRANSFERS IN WHOLE, BUT NOT IN PART, TO NOMINEES OF DTC OR TO A SUCCESSOR THEREOF OR SUCH SUCCESSOR'S NOMINEE AND TRANSFERS OF PORTIONS OF THIS GLOBAL SECURITY SHALL BE LIMITED TO TRANSFERS MADE IN ACCORDANCE WITH THE RESTRICTIONS SET FORTH IN THE INDENTURE REFERRED TO ON THE REVERSE HEREOF.

[Restricted Notes Legend]

THE SECURITY EVIDENCED BY THIS CERTIFICATE HAS NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "SECURITIES ACT OF 1933"), OR ANY STATE SECURITIES LAWS, AND MAY NOT BE OFFERED OR SOLD EXCEPT AS SET FORTH IN THE FOLLOWING SENTENCE. BY ACQUISITION HEREOF OR OF A BENEFICIAL INTEREST HEREIN, THE HOLDER AGREES (1) THAT IT WILL NOT PRIOR TO THE DATE TWO YEARS AFTER THE LAST DATE OF ORIGINAL ISSUANCE OF THE 2 5/8 % CONVERTIBLE SUBORDINATED NOTES DUE 2027 OF ISIS PHARMACEUTICALS, INC. (THE "COMPANY") RESELL OR OTHERWISE TRANSFER THE SECURITY EVIDENCED HEREBY OR THE COMMON STOCK THAT MAY BE ISSUABLE UPON CONVERSION OF SUCH SECURITY EXCEPT (A) TO THE COMPANY OR ANY SUBSIDIARY THEREOF, (B) TO A PERSON IT REASONABLY BELIEVES IS A QUALIFIED INSTITUTIONAL BUYER IN COMPLIANCE WITH RULE 144A UNDER THE SECURITIES ACT OF 1933, (C) PURSUANT TO A REGISTRATION STATEMENT WHICH HAS BEEN DECLARED EFFECTIVE UNDER THE SECURITIES ACT OF 1933 AND WHICH CONTINUES TO BE EFFECTIVE AT THE TIME OF SUCH TRANSFER, OR (D) PURSUANT TO THE EXEMPTION FROM REGISTRATION REQUIREMENTS UNDER THE SECURITIES ACT OF 1933 PROVIDED BY RULE 144, IF AVAILABLE, SUBJECT TO THE COMPANY'S AND THE TRUSTEE'S

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RIGHT PRIOR TO ANY SUCH TRANSFER, TO REQUIRE THE DELIVERY OF AN OPINION OF COUNSEL, CERTIFICATIONS AND/OR OTHER INFORMATION SATISFACTORY TO THE COMPANY AND THE TRUSTEE; AND (2) THAT IT WILL DELIVER TO EACH PERSON TO WHOM THE SECURITY EVIDENCED HEREBY IS TRANSFERRED PURSUANT TO CLAUSE 1(B) ABOVE A NOTICE SUBSTANTIALLY TO THE EFFECT OF THIS LEGEND.

2

No.

\$

2 5/8 % Convertible Subordinated Note due 2027

CUSIP No.: 464337AD6

Isis Pharmaceuticals, Inc., a Delaware corporation, promises to pay to [Cede & Co., or registered assigns](1) , principal sum of , Dollars [, as revised by the Schedule of Increases or Decreases in Global Note attached hereto,](2) on February 15, 2027.

Interest Payment Dates: February 15 and August 15.

Record Dates: February 1 and August 1.

Reference is made to the further provisions of this Note set forth on the reverse hereof, including, without limitation, provisions giving the holder of this Note the right to convert this Note into cash and, if applicable, Common Stock, on the terms and subject to the limitations referred to on the reverse hereof and as more fully specified in the Indenture. Such further provisions shall for all purposes have the same effect as though fully set forth at this place.

This Note shall not be valid or become obligatory for any purpose until the certificate of authentication hereon shall have been manually signed by the Trustee or a duly authorized authenticating agent under the Indenture.

IN WITNESS WHEREOF, Isis Pharmaceuticals, Inc. has caused this instrument to be duly executed.

ISIS PHARMACEUTICALS, INC.,

By: _____

Name:

Title:

Dated:

TRUSTEE'S CERTIFICATE OF
AUTHENTICATION

WELLS FARGO BANK, N.A.,

as Trustee, certifies that this is one of the Notes referred
to in the Indenture.

- _____
(1) Use the Schedule of Increases and Decreases language if Note is in Global form.
(2) Use the Schedule of Increases and Decreases language if Note is in Global form.

1

By: _____

Authorized Signatory

2

[FORM OF REVERSE SIDE OF NOTE]

2 ⁵/₈ % Convertible Subordinated Note due 2027

1. Interest

(a) ISIS PHARMACEUTICALS, INC., a Delaware corporation (such corporation, and its successors and assigns under the Indenture hereinafter referred to, being herein called the "Company"), promises to pay interest on the principal amount of this Note at the rate per annum shown above. The Company will pay interest semiannually on February 15 and August 15 of each year commencing on August 15, 2007. Interest on the Notes will accrue from the most recent date to which interest has been paid or, if no interest has been paid, from January 23, 2007. Interest will be computed on the basis of a 360-day year of twelve 30-day months. If a payment date is not a Business Day, payment will be made on the next succeeding Business Day, and no additional interest will accrue in respect of such payment by virtue of the payment being made on such later date.

(b) Additional Interest. The holder of this Note is entitled to the benefits of a Registration Rights Agreement, dated as of January 23, 2007, by and between the Company and Lehman Brothers Inc., as representative of the Initial Purchasers (the "Registration Rights Agreement"). Capitalized terms used in this paragraph (b) but not defined herein have the meanings assigned to them in the Registration Rights Agreement. In the event of a Registration Default under the Registration Rights Agreement, the Company shall pay Additional Interest on Notes that constitute Transfer Restricted Securities from and including the day following the Registration Default to but excluding the day on which the Registration Default has been cured, accruing at a rate, (x) with respect to the first 90-day period during which a Registration Default shall have occurred and be continuing, equal to 0.25% per annum of the principal amount of the Notes, and (y) with respect to the period commencing on the 91st day following the day the Registration Default shall have occurred and be continuing, equal to 0.50% per annum of the principal amount of the Notes; provided that in no event shall Additional Interest accrue at an aggregate rate per year exceeding 0.50% of the principal amount of the Notes and provided further that Additional Interest with respect to such Transferred Restricted Securities shall not accrue under more than one of clauses (i), (ii), (iii) and (iv) of Section 3(a) of the Registration Rights Agreement at any one time. No Additional Interest shall be payable on any Notes that have been converted into shares of Common Stock or such Common Stock.

(c) To the extent elected by the Company, the sole remedy for an Event of Default relating to the failure by the Company to comply with Section 4.03 of the Indenture, for the first 120 days after the occurrence of such an Event of Default shall consist exclusively of the right to receive special interest on the Notes at an annual rate equal to 0.25% of the Principal amount of the Notes ("Special Interest"). In no event shall the Special Interest, together with any Additional Interest payable pursuant to the Registration Rights Agreement, accrue at an aggregate annual rate exceeding 0.50% of the Principal amount of the Notes.

(d) Except as otherwise specifically set forth, all references herein to "interest" include deferred interest, Special Interest and Additional Interest, if any.

2. Method of Payment

The Company will pay interest on the Notes (except defaulted interest) to the Persons who are registered Noteholders at the close of business on the February 1 and August 1 next preceding the interest payment date even if Notes are canceled after the record date and on or before the interest payment date, except as otherwise provided in the Indenture. Holders must surrender Notes to a Paying Agent to collect Principal payments. The Company will pay Principal and interest in money of the United States of America that at the time of payment is legal tender for payment of public and private debts. The Company shall pay interest (i) on any Global Notes by wire transfer of immediately available funds to the account of the Depository or its nominee, (ii) on any Notes in certificated form having a principal amount of less than \$2,000,000, by check mailed to the address of the Person entitled thereto as it appears in the Register, provided, however, that at maturity interest will be payable at the office of the Company maintained by the Company for such purposes, which shall initially be an office or agency of the Trustee (as defined below) and (iii) on any Notes in certificated form having a Principal amount of \$2,000,000 or more, by wire transfer in immediately available funds at the election of the holder of such Notes duly delivered to the Trustee at least five Business Days prior to the relevant interest payment date, provided, however, that at maturity interest will be payable at the office of the Company maintained by the Company for such purposes, which shall initially be an office or agency of the Trustee.

3. Paying Agent and Registrar

Initially, Wells Fargo Bank, N.A., a national banking association (the "Trustee"), will act as Paying Agent, Registrar and conversion agent. The Company may appoint and change any Paying Agent, Registrar or co-registrar or conversion agent without notice. The Company or any of its domestically incorporated Wholly Owned Subsidiaries may act as Paying Agent, Registrar or co-registrar, or conversion agent.

4. Indenture

The Company issued the Notes under an Indenture dated as of January 23, 2007 (the "Indenture"), among the Company and the Trustee. The terms of the Notes include those stated in the Indenture and those made part of the Indenture by reference to the Trust Indenture Act of 1939 (15 U.S.C. §§ 77aaa-77bbb) as in effect on the date of the Indenture (the "TIA"). Terms defined in the Indenture and not defined herein have the meanings ascribed thereto in the Indenture (except as specifically provided in Section 1(b) hereof). The Notes are subject to all such terms, and Noteholders are referred to the Indenture and the TIA for a statement of those terms.

The Notes are subordinated unsecured obligations of the Company. This Note is one of the Notes referred to in the Indenture issued in an aggregate principal amount of \$125,000,000 (up to \$162,500,000 if the option of the Initial Purchasers to purchase additional Notes is exercised in full). The Indenture also imposes limitations on the ability of the Company to consolidate or merge with or into any other Person or convey, transfer or lease all or substantially all of the property of the Company.

5. Optional Redemption

The Notes will not be redeemable at the option of the Company prior to February 15, 2012. At any time on or after February 15, 2012, the Notes will be redeemable at the option of the Company, in whole or in part, on not less than 30 calendar days' nor more than 60 calendar days' prior notice, at the redemption prices set forth in the Indenture, plus accrued and unpaid interest to the redemption date (subject to the right of holders of record on the relevant record date to receive interest due on the relevant interest payment date).

6. Sinking Fund

The Notes are not subject to any sinking fund.

7. Notice of Redemption

Notice of redemption will be delivered at least 30 calendar days but not more than 60 calendar days before the redemption date to each holder of Notes to be redeemed at his or her registered address. Notes in denominations larger than \$1,000 may be redeemed in part but only in whole multiples of \$1,000. If money sufficient to pay the redemption price of and accrued interest on all Notes (or portions thereof) to be redeemed on the redemption date is deposited with the Paying Agent on or before the redemption date and certain other conditions are satisfied, on and after such date interest ceases to accrue on such Notes (or such portions thereof) called for redemption.

8. Repurchase of Notes at the Option of Noteholders

If a Fundamental Change occurs at any time prior to the Maturity Date of the Notes, this Note will be subject to a repurchase, at the option of the holder, on a Fundamental Change Repurchase Date, specified by the Company, that is not less than 15 calendar days nor more than 35 calendar days after notice thereof, at a repurchase price equal to 100% of the Principal amount hereof, together with accrued and unpaid interest on this Note to, but excluding, the Fundamental Change Repurchase Date; provided that if such Fundamental Change Repurchase Date falls after a record date and on or prior the corresponding interest payment date, the accrued and unpaid interest shall be payable to the holder of record of this Note on the preceding February 1 or August 1, as the case may be. The Notes submitted for repurchase must be \$1,000 in principal amount or whole multiples thereof. The Company shall deliver to all holders of record of the Notes (and to beneficial owners as required by applicable law) a notice of the occurrence of a Fundamental Change and of the repurchase right arising as a result within 20 calendar days after the occurrence of such Fundamental Change. For Notes to be so repurchased at the option of the holder, the holder must deliver to the Paying Agent in accordance with the terms of the Indenture, the Repurchase Notice containing the information specified by the Indenture, together with such Notes, duly endorsed for transfer, or (if the Notes are Global Notes) book-entry transfer of the Notes, prior to 5:00 p.m., New York City time, on the Business Day immediately preceding the Fundamental Change Repurchase Date. The repurchase price must be paid in cash.

Subject to the terms and conditions of the Indenture, each holder shall have the right, at such holder's option, to require the Company to repurchase all or any portion of the Notes held

by such holder, on February 15, 2014, February 15, 2017 and February 15, 2022 at a repurchase price equal to 100% of the Principal amount of this Note, together with any accrued and unpaid interest on this Note to, but excluding, the Repurchase Date, as provided in the Indenture. To exercise such right, a holder shall deliver to the Paying Agent the Repurchase Notice containing the information specified by the Indenture, together with the Notes, duly endorsed for transfer, or (if the Notes are Global Notes) book-entry transfer of the Notes, at any time during the period from 9:00 a.m., New York City time, on the date that is 20 Business Days prior to the applicable Repurchase Date to 5:00 p.m., New York City time, on the Business Day immediately preceding the applicable Repurchase Date. The repurchase price must be paid in cash.

Holders have the right to withdraw any Repurchase Notice by delivering to the Paying Agent a written notice of withdrawal at any time prior to 5:00 p.m., New York City time, on the Business Day immediately preceding the Fundamental Change Repurchase Date or the Repurchase Date, as applicable, all as provided in the Indenture.

If cash sufficient to pay the repurchase price of and accrued and unpaid interest, if any, on all Notes or portions thereof to be repurchased as of the Fundamental Change Repurchase Date or Repurchase Date, as the case may be, is deposited with the Paying Agent, on the Fundamental Change Repurchase Date or on the Repurchase Date, as the case may be, then such Notes will cease to be outstanding and interest will cease to accrue on such Notes immediately thereafter, and the holder thereof shall have no other rights as such other than the right to receive the repurchase price upon surrender of such Notes.

9. Conversion

Upon the occurrence of certain events specified in the Indenture and in compliance with the provisions of the Indenture, on or prior to the close of business on the Trading Day immediately preceding the Maturity Date of this Note, the holder hereof has the right, at its option, to convert each \$1,000 principal amount of this Note into cash and, if applicable, Common Stock based on a Conversion Rate of 68.3761 shares of Common Stock per \$1,000 principal amount of Notes (a conversion price of approximately \$14.63 per share), as the same may be adjusted pursuant to the terms of the Indenture, as such shares shall be constituted at the date of conversion, upon surrender of this Note (if in certificated form) with the form entitled "Conversion Notice" on the reverse hereof duly completed and manually signed, to the Company at the office or agency of the Company maintained for that purpose in accordance with the terms of the Indenture, or at the option of such holder, the Corporate Trust Office, together with any funds required pursuant to the terms of the Indenture, and, unless any shares issuable on conversion are to be issued in the same name as this Note, duly endorsed by, or accompanied by instruments of transfer in form satisfactory to the Company duly executed by, the holder or by such holder's duly authorized attorney. The Company will notify the holder thereof of any event triggering the right to convert the Notes as specified above in accordance with the Indenture. In order to exercise the conversion right with respect to any interest in a Global Note, the holder must complete the appropriate instruction form pursuant to the Depository's book-entry conversion program, deliver by book-entry delivery an interest in such Global Note, furnish appropriate endorsements and transfer documents if required by the Company or the Trustee or conversion agent, and pay the funds, if any, required pursuant to the terms of the Indenture. As specified in the Indenture, upon conversion, the Company may pay cash, shares of Common

Stock or any combination thereof, based on the Conversion Value (as defined in the Indenture) calculated using the Daily Conversion Values during the Conversion Period (as defined in the Indenture). At any time on or prior to the 26th Trading Day preceding the Maturity Date, the Company may irrevocably elect to satisfy in cash its conversion obligations with respect to the Principal amount converted.

If and only to the extent holders elect to convert the Notes in connection with a Non-Stock Change of Control (as defined in the Indenture), the Company will increase the Conversion Rate applicable to such converting Notes; provided that in the case of a Non-Stock Change of Control constituting a Public Acquirer Change of Control (as defined in the Indenture), the Company may, in lieu of increasing the Conversion Rate, elect to adjust the conversion obligation and the Conversion Rate such that from and after the effective date of such Public Acquirer Change of Control, Noteholders will be entitled to convert their Notes (subject to the satisfaction of certain conditions) into a number of shares of Public Acquirer's Common Stock (as defined in the Indenture) determined as set forth in the Indenture.

No adjustment in respect of interest on any Notes converted or dividends on any shares issued upon conversion of such Notes will be made upon any conversion except as set forth in the next sentence, but holders who convert their Notes will receive on the next interest payment day any Additional Interest accrued through the Conversion Date. If this Note (or portion hereof) is surrendered for conversion during the period from the 5:00 p.m., New York City time, on any applicable Record Date for the payment of interest to 5:00 p.m., New York City time, on the Business Day preceding the corresponding interest payment date, this Note (or portion hereof being converted) must be accompanied by payment, in immediately available funds or other funds acceptable to the Company, of an amount equal to the interest (excluding any Additional Interest) otherwise payable on such interest payment date on the principal amount being converted; provided that no such payment shall be required (1) if the holder surrenders this Note for conversion in connection with a redemption and the Company has specified a redemption date that is after a Record Date and on or prior to the corresponding interest payment date, (2) if the holder surrenders this Note in connection with a Fundamental Change and the Company has specified a Fundamental Change Repurchase Date that is after a Record Date and on or prior to the corresponding interest payment date or (3) to the extent of any overdue interest, if any, existing at the time of conversion with respect to this Note.

No fractional shares will be issued upon any conversion of Notes, but an adjustment and payment in cash will be made, as provided in the Indenture, in respect of any fraction of a share which would otherwise be issuable upon the surrender of any Notes for conversion.

A Note in respect of which a holder is exercising its right to require repurchase may be converted only if such holder validly withdraws its election to exercise such right to require repurchase in accordance with the terms of the Indenture.

10. Denominations, Transfer, Exchange

The Notes are in registered form without coupons in denominations of \$1,000 and whole multiples of \$1,000. A Noteholder may transfer or exchange Notes in accordance with the Indenture. Upon any transfer or exchange, the Registrar and the Trustee may require a

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Noteholder, among other things, to furnish appropriate endorsements or transfer documents and to pay any taxes required by law or permitted by the Indenture. The Registrar need not issue, register the transfer of, or exchange any Notes during the period of 15 days before the mailing of the notice of redemption, or register the transfer of or exchange any Notes so selected for redemption, in whole or in part, except the unredeemed portion of any Notes being redeemed in part.

11. Persons Deemed Owners

The registered holder of this Note may be treated as the owner of it for all purposes.

12. Unclaimed Money

Subject to any applicable abandoned property law, the Trustee and the Paying Agent shall pay to the Company upon written request any money held by them for the payment of Principal or interest and any shares of Common Stock or other property due in respect of converted Notes that remains unclaimed for two years, and, thereafter, Noteholders entitled to the money and/or securities must look to the Company for payment as general creditors.

13. Amendment, Waiver

Subject to certain exceptions set forth in the Indenture, (a) the Indenture or the Notes may be amended without prior notice to any Noteholder but with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding Notes and (b) any Default or noncompliance with any provision may be waived with the written consent of the holders of at least a majority in principal amount of the outstanding Notes. Subject to certain exceptions set forth in the Indenture, without the consent of any holder of Notes, the Company and the Trustee may amend the Indenture or the Notes (i) to provide for conversion rights of Noteholders and the Company's repurchase obligations in connection with a Fundamental Change in the event of any reclassification of the Common Stock, merger or consolidation, or sale, conveyance, transfer or lease of the Company's property and assets substantially as an entirety; (ii) to secure the Notes; (iii) to provide for the assumption of the Company's obligations in the event of a merger or consolidation, or sale, conveyance, transfer or lease of the Company's property and assets substantially as an entirety; (iv) to surrender any right or power conferred upon the Company; (v) to add to the covenants of the Company for the benefit of the Noteholders; (vi) to cure any ambiguity or correct or supplement any inconsistent or otherwise defective provision contained in this Indenture; provided that such modification or amendment does not adversely affect the interests of the Noteholders in any material respect; (vii) to make any provision with respect to matters or questions arising under the Indenture that the Company may deem necessary or desirable and that shall not be inconsistent with provisions of this Indenture; provided that such change or modification does not, in the good faith opinion of the Board of Directors, adversely affect the interests of the Noteholders in any material respect; (viii) to provide for uncertificated Notes in addition to or in place of certificated Notes; provided, however, that the uncertificated Notes are issued in registered form for purposes of Section 163(f) of the Code or in a manner such that the uncertificated Notes are described in Section 163(f)(2)(B) of the Code; (ix) to increase the conversion rate; provided, that the increase will not adversely affect the interests of the Noteholders; (x) to make any change in Article 12 that would limit or terminate the benefits

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available to any holder of Senior Indebtedness (or Representatives therefor) under Article 12; (xi) to comply with any requirements of the SEC in connection with qualifying, or maintaining the qualification of, this Indenture under the TIA; (xii) to add Guarantees with respect to the Notes; (xiii) to make any changes or modifications necessary in connection with the registration of the Notes under the Securities Act as contemplated in the Registration Rights Agreement; provided that such change or modification does not adversely affect the interests of the Noteholders in any material respect; or (xiv) to provide for a successor Trustee.

14. Defaults and Remedies

If an Event of Default occurs (other than (x) an Event of Default relating to Section 4.03 of the Indenture as described below and (y) an Event of Default relating to certain events of bankruptcy, insolvency or reorganization of the Company) and is continuing, the Trustee or the holders of at least 25% in Principal amount of the outstanding Notes may declare the Principal of and accrued but unpaid interest on all the Notes to be due and payable. If an Event of Default relating to certain events of bankruptcy, insolvency or reorganization of the Company occurs, the principal of and interest on all the Notes will become immediately due and payable without any declaration or other act on the part of the Trustee or any Noteholders. Under certain circumstances, the holders of a majority in Principal amount of the outstanding Notes may rescind any such acceleration with respect to the Notes and its consequences.

If an Event of Default occurs and is continuing, the Trustee will be under no obligation to exercise any of the rights or powers under the Indenture at the request or direction of any of the Noteholders unless such Noteholders have offered to the Trustee reasonable indemnity or security against any loss, liability or expense. Subject to certain exceptions, no Noteholder may pursue any remedy with respect to the Indenture or the Notes unless (i) such Noteholder has previously given the Trustee notice that an Event of Default is continuing, (ii) holders of at least 25% in Principal amount of the outstanding Notes have requested the Trustee in writing to pursue the remedy, (iii) such Noteholders have offered the Trustee reasonable security or indemnity against any loss, liability or expense, (iv) the Trustee has not complied with such request within 60 days after the receipt of the request and the offer of security or indemnity and (v) the holders of a majority in Principal amount of the outstanding Notes have not given the Trustee a direction inconsistent with such request within such 60-day period. Subject to certain restrictions, the holders of a majority in Principal amount of the outstanding Notes are given the right to direct the time, method and place of conducting any proceeding for any remedy available to the Trustee or of exercising any trust or power conferred on the Trustee. The Trustee, however, may refuse to follow any direction that conflicts with law or the Indenture or that the Trustee determines is unduly prejudicial

to the rights of any other Noteholder or that would involve the Trustee in personal liability. Prior to taking any action under the Indenture, the Trustee will be entitled to indemnification satisfactory to it in its sole discretion against all losses and expenses caused by taking or not taking such action.

Notwithstanding anything herein to the contrary, to the extent elected by the Company, the sole remedy for an Event of Default relating to the failure by the Company to comply with Section 4.03 of the Indenture, for the first 120 days after the occurrence of such an Event of Default shall consist exclusively of the right to receive Special Interest on the Notes at an annual rate equal to 0.25% of the Principal amount of the Notes. Thereafter, or in the event the

Company does not elect to pay Special Interest upon an Event of Default relating to reporting obligations in Section 4.03 of the Indenture, the Notes shall be subject to acceleration as provided in the first paragraph of this Section 14 without giving effect to clause (x) in the parenthetical of the first sentence.

No reference herein to the Indenture and no provision of this Note or of the Indenture shall impair, as among the Company and the holder of the Notes, the obligation of the Company, which is absolute and unconditional, to pay the Principal of, premium, if any, on and interest on this Note at the place, at the respective times, at the rate and in the coin or currency herein and in the Indenture prescribed.

15. Subordination.

The Notes are subordinated to all Senior Indebtedness of the Company. Each holder of this Note, whether upon original issue or upon registration of transfer, assignment or exchange thereof, by accepting the same, agrees to the subordination provisions set forth in Article 12 of the Indenture and authorizes the Trustee on its behalf to take such action as may be necessary or appropriate to effectuate the subordination so provided and appoints the Trustee his attorney-in-fact for any and all such purposes.

No reference herein to the subordination provisions of the Indenture and no provision of this Note or of the Indenture shall alter or impair the obligation of the Company, which is absolute and unconditional, to pay the principal of, interest on this Note and Additional Interest, if any, at the place, at the respective times, at the rate and in the coin or currency herein prescribed.

16. Trustee Dealings with the Company.

Subject to certain limitations imposed by the TIA, the Trustee under the Indenture, in its individual or any other capacity, may become the owner or pledgee of Notes and may otherwise deal with and collect obligations owed to it by the Company or its Affiliates and may otherwise deal with the Company or its Affiliates with the same rights it would have if it were not Trustee.

17. No Recourse Against Others

A director, officer, employee or stockholder, as such, of the Company shall not have any liability for any obligations of the Company under the Notes or the Indenture or for any claim based on, in respect of or by reason of such obligations or their creation. By accepting a Note, each Noteholder waives and releases all such liability. The waiver and release are part of the consideration for the issue of the Notes.

18. Authentication

This Note shall not be valid until an authorized signatory of the Trustee (or an authenticating agent) manually signs the certificate of authentication on the other side of this Note.

19. Abbreviations

Customary abbreviations may be used in the name of a Noteholder or an assignee, such as TEN COM (=tenants in common), TEN ENT (=tenants by the entireties), JT TEN (=joint tenants with rights of survivorship and not as tenants in common), CUST (=custodian), and U/G/M/A (=Uniform Gift to Minors Act).

20. GOVERNING LAW

THIS NOTE SHALL BE GOVERNED BY, AND CONSTRUED IN ACCORDANCE WITH, THE LAWS OF THE STATE OF NEW YORK.

21. CUSIP and ISIN Numbers

Pursuant to a recommendation promulgated by the Committee on Uniform Security Identification Procedures, the Company has caused CUSIP and ISIN numbers to be printed on the Notes and has directed the Trustee to use CUSIP and ISIN numbers in notices of redemption as a convenience to Noteholders. No representation is made as to the accuracy of such numbers either as printed on the Notes or as contained in any notice of redemption and reliance may be placed only on the other identification numbers placed thereon.

The Company will furnish to any holder of Notes upon written request and without charge to the holder a copy of the Indenture which has in it the text of this Note.

CONVERSION NOTICE

TO: ISIS PHARMACEUTICALS, INC.; WELLS FARGO BANK, N.A., as Trustee

The undersigned registered owner of this Note hereby irrevocably exercises the option to convert this Note, or the portion thereof (which is \$1,000 or a multiple thereof) below designated, into, cash and shares of Common Stock of Isis Pharmaceuticals, Inc., if any, in accordance with the terms of the Indenture referred to in this Note, and directs that the check in payment for cash and the shares, if any, issuable and deliverable upon such conversion, deliverable upon conversion or for fractional shares and any Notes representing any unconverted principal amount hereof, be issued and delivered to the registered holder hereof unless a different name has been indicated below. Capitalized terms used herein but not defined shall have the meanings ascribed to such terms in the Indenture. If shares or any portion of this Note not converted are to be issued in the name of a person other than the undersigned, the undersigned will provide the appropriate information below and pay all transfer taxes payable with respect thereto. Any amount required to be paid by the undersigned on account of interest accompanies this Note.

Dated: _____

Signature(s)

Signature(s) must be guaranteed by an "eligible guarantor institution" meeting the requirements of the Registrar, which requirements include membership or participation in the Security Transfer Agent Medallion Program ("STAMP") or such other "signature guarantee program" as may be determined by the Registrar in addition to, or in substitution for, STAMP, all in accordance with the Securities Exchange Act of 1934, as amended.

Signature Guarantee

Fill in the registration of shares of Common Stock, if any, if to be issued, and Notes if to be delivered, and the person to whom cash, if any, and payment for fractional shares is to be made, if to be made, other than to and in the name of the registered holder:

Please print name and address

(Name)

(Street Address)

(City, State and Zip Code)

Principal amount to be converted
(if less than all):

\$

Social Security or Other Taxpayer
Identification Number:

NOTICE: The signature on this Conversion Notice must correspond with the name as written upon the face of the Notes in every particular without alteration or enlargement or any change whatever.

REPURCHASE NOTICE

TO: ISIS PHARMACEUTICALS, INC., WELLS FARGO BANK N.A., as Trustee

The undersigned registered owner of this Note hereby irrevocably acknowledges receipt of a notice from Isis Pharmaceuticals, Inc. (the "Company") regarding the right of holders to elect to require the Company to repurchase the Notes and requests and instructs the Company to repay the entire principal amount of this Note, or the portion thereof (which is \$1,000 or an integral multiple thereof) below designated, in accordance with the terms of the Indenture at

the price of 100% of such entire principal amount or portion thereof, together with accrued and unpaid interest to, but excluding, the Repurchase Date or the Fundamental Change Repurchase Date, as the case may be, to the registered holder hereof. Capitalized terms used herein but not defined shall have the meanings ascribed to such terms in the Indenture. The Notes shall be repurchased by the Company as of the Repurchase Date or the Fundamental Change Repurchase Date, as the case may be, pursuant to the terms and conditions specified in the Indenture.

Dated: _____

Signature(s): _____

NOTICE: The above signatures of the holder(s) hereof must correspond with the name as written upon the face of the Notes in every particular without alteration or enlargement or any change whatever.

Notes Certificate Number (if applicable):

Principal amount to be repurchased (if less than all, must be \$1,000 or whole multiples thereof):

Social Security or Other Taxpayer Identification Number:

ASSIGNMENT

For value received _____ hereby sell(s) assign(s) and transfer(s) unto _____ (Please insert social security or other Taxpayer Identification Number of assignee) the within Notes, and hereby irrevocably constitutes and appoints _____ attorney to transfer said Notes on the books of the Company, with full power of substitution in the premises.

In connection with any transfer of the Notes prior to the expiration of the holding period applicable to sales thereof under Rule 144(k) under the Securities Act (or any successor provision) (other than any transfer pursuant to a registration statement that has been declared effective under the Securities Act), the undersigned confirms that such Notes are being transferred:

- o To Isis Pharmaceuticals, Inc. or a subsidiary thereof; or
- o To a "qualified institutional buyer" in compliance with Rule 144A under the Securities Act of 1933, as amended; or
- o Pursuant to and in compliance with Rule 144 under the Securities Act of 1933, as amended; or
- o Pursuant to a Registration Statement which has been declared effective under the Securities Act of 1933, as amended, and which continues to be effective at the time of transfer;

and unless the Notes has been transferred to Isis Pharmaceuticals, Inc. or a subsidiary thereof, the undersigned confirms that such Notes are not being transferred to an "affiliate" of the Company as defined in Rule 144 under the Securities Act of 1933, as amended.

Unless one of the boxes is checked, the Trustee will refuse to register any of the Notes evidenced by this certificate in the name of any person other than the registered holder thereof.

Dated: _____

Signature(s)

Signature(s) must be guaranteed by an "eligible guarantor institution" meeting the requirements of the Registrar, which requirements include membership or participation in the Security Transfer Agent Medallion Program ("STAMP") or such other "signature guarantee program" as may be determined by the Registrar in addition to, or in

substitution for, STAMP, all in accordance with the Securities Exchange Act of 1934, as amended.

Signature Guarantee

SCHEDULE OF INCREASES AND DECREASES IN GLOBAL NOTE(3)

The following increases or decreases in this Global Note have been made:

<u>Date</u>	<u>Amount of decrease in Principal Amount of this Global Note</u>	<u>Amount of increase in Principal Amount of this Global Note</u>	<u>Principal Amount of Note following such decrease or increase</u>	<u>Signature of authorized signatory of Trustee or Securities Custodian</u>

(3) For Global Notes only

EXHIBIT B

**FORM OF RESTRICTIVE LEGEND FOR
COMMON STOCK ISSUED UPON CONVERSION(4)**

THE SECURITY EVIDENCED BY THIS CERTIFICATE HAS NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE "SECURITIES ACT OF 1933"), OR ANY STATE SECURITIES LAWS, AND MAY NOT BE OFFERED OR SOLD EXCEPT AS SET FORTH IN THE FOLLOWING SENTENCE BY ACQUISITION HEREOF. THE HOLDER AGREES THAT (1) IT WILL NOT, WITHIN TWO YEARS AFTER THE LAST DATE OF ORIGINAL ISSUANCE OF THE SECURITY UPON THE CONVERSION OF WHICH THE COMMON STOCK EVIDENCED HEREBY WAS ISSUED, RESELL OR OTHERWISE TRANSFER THE SECURITY EVIDENCED HEREBY EXCEPT (A) TO ISIS PHARMACEUTICALS, INC. (THE "COMPANY") OR ANY SUBSIDIARY THEREOF, (B) TO A PERSON IT REASONABLY BELIEVES IS A QUALIFIED INSTITUTIONAL BUYER IN COMPLIANCE WITH RULE 144A UNDER THE SECURITIES ACT OF 1933, (C) PURSUANT TO A REGISTRATION STATEMENT WHICH HAS BEEN DECLARED EFFECTIVE UNDER THE SECURITIES ACT OF 1933 AND WHICH CONTINUES TO BE EFFECTIVE AT THE TIME OF SUCH TRANSFER, OR (D) PURSUANT TO THE EXEMPTION FROM REGISTRATION REQUIREMENTS UNDER THE SECURITIES ACT OF 1933 PROVIDED BY RULE 144, IF AVAILABLE, SUBJECT TO THE COMPANY'S RIGHT PRIOR TO ANY SUCH TRANSFER, TO REQUIRE THE DELIVERY OF AN OPINION OF COUNSEL, CERTIFICATIONS AND/OR OTHER INFORMATION SATISFACTORY TO THE COMPANY; AND (2) THAT IT WILL DELIVER TO EACH PERSON TO WHOM THE SECURITY EVIDENCED HEREBY IS TRANSFERRED PURSUANT TO CLAUSE 2(B) ABOVE A NOTICE SUBSTANTIALLY TO THE EFFECT OF THIS LEGEND.

(4) This legend should be included only if the Security is a Transfer Restricted Security.

REGISTRATION RIGHTS AGREEMENT

BY AND BETWEEN

ISIS PHARMACEUTICALS, INC.,

AS ISSUER

AND

LEHMAN BROTHERS INC.,

AS REPRESENTATIVE OF THE INITIAL PURCHASERS

DATED AS OF JANUARY 23, 2007

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REGISTRATION RIGHTS AGREEMENT, dated as of January 23, 2007, by and among Isis Pharmaceuticals, Inc. (together with any successor entity, herein referred to as the “**Issuer**”), and Lehman Brothers Inc., as representative (the “**Representative**”) of the initial purchasers attached hereto on Schedule I (collectively, the “**Initial Purchasers**”).

Pursuant to the Purchase Agreement, dated January 17, 2007, among the Issuer and the Representative, as representative of the Initial Purchasers (the “**Purchase Agreement**”), the Initial Purchasers have agreed to purchase from the Issuer up to \$125,000,000 aggregate principal amount 2^{5/8}% Convertible Subordinated Notes due 2027 (the “**Notes**”) (or up to \$162,500,000 aggregate principal amount if the Initial Purchasers exercise in full their option to purchase additional Notes, as set forth in the Purchase Agreement). The Notes initially may be convertible into fully paid, nonassessable common stock, \$0.001 par value per share, of the Issuer (the “**Common Stock**”) on the terms, and subject to the conditions, set forth in the Indenture (as defined herein). To induce the Initial Purchasers to purchase the Notes, the Issuer has agreed to provide the registration rights set forth in this Agreement pursuant to the Purchase Agreement.

The parties hereby agree as follows:

1. Definitions. As used in this Agreement, the following capitalized terms shall have the following meanings:

Additional Interest: As defined in Section 3(a) hereof.

Additional Interest Payment Date: Each February 15 and August 15, commencing August 15, 2007.

Agreement: This Registration Rights Agreement, as amended, modified or otherwise supplemented from time to time in accordance with the terms hereof.

Broker-Dealer: Any broker or dealer registered under the Exchange Act.

Business Day: A day other than a Saturday or Sunday or any day on which banking institutions in The City of New York are authorized or obligated by law or executive order to close.

Commission: Securities and Exchange Commission.

Common Stock: As defined in the preamble hereto.

Effectiveness Period: As defined in Section 2(a)(iii) hereof.

Effectiveness Target Date: As defined in Section 2(a)(ii) hereof.

Exchange Act: Securities Exchange Act of 1934, as amended, and the rules and regulations of the Commission thereunder.

Holder: A Person who owns, beneficially or otherwise, Transfer Restricted Securities.

Indemnified Holder: As defined in Section 6(a) hereof.

Indenture: The Indenture, dated as of January 23, 2007, among the Issuer and Trustee, pursuant to which the Notes are to be issued, as such Indenture is amended, modified or supplemented from time to time in accordance with the terms thereof.

Initial Purchasers: As defined in the preamble hereto.

Issuer: As defined in the preamble hereto.

Majority of Holders: Registered Holders of a number of shares of the then outstanding Common Stock constituting Transfer Restricted Securities and an aggregate principal amount of then outstanding Notes constituting Transfer Restricted Securities, such that the sum of such shares of Common Stock and the shares of Common Stock issuable upon conversion of such Notes constitute in excess of 50% of the sum of all of the then outstanding shares of Common Stock constituting Transfer Restricted Securities and the number of shares of Common Stock issuable upon conversion of then outstanding Notes constituting Transfer Restricted Securities, in each case assuming that the Notes are then convertible and that no cash is paid upon a conversion of Notes. For purposes of the immediately preceding sentence, (i) any Holder may elect to make any request, notice, demand, objection or other action hereunder with respect to all or any portion of Transfer Restricted Securities held by it and only the portion as to which such action is taken shall be included in the numerator of the fraction described in the preceding sentence and (ii) Transfer Restricted Securities owned, directly or indirectly, by the Issuer or its Affiliates shall be deemed not to be outstanding.

NASD: National Association of Securities Dealers, Inc.

New Securities: As defined in Section 10(d).

Notes: As defined in the preamble hereto.

Offering Memorandum: The Offering Memorandum relating to the offer of the Notes dated January 17, 2007.

Person: An individual, partnership, corporation, unincorporated organization, limited liability company, trust, joint venture or a government or agency or political subdivision thereof.

Prospectus: The prospectus included in a Shelf Registration Statement (including, without limitation, a prospectus that discloses information previously omitted from a prospectus filed as part of an effective registration statement in reliance upon Rule 430A promulgated pursuant to the Securities Act), as amended or supplemented by any prospectus supplement and by all other amendments thereto, including post-effective amendments, and all material incorporated by reference into such Prospectus.

Purchase Agreement: As defined in the preamble hereto.

Questionnaire: As defined in Section 2(b) hereof.

Questionnaire Deadline: As defined in Section 2(b) hereof.

Record Holder: With respect to any Additional Interest Payment Date, each Person who is a Holder on the record date with respect to such Additional Interest Payment Date, which record date shall be the date that is the 15th day preceding the relevant Additional Interest Payment Date.

Registration Default: As defined in Section 3(a) hereof.

Securities Act: Securities Act of 1933, as amended, and the rules and resolutions of the Commission thereunder.

Shelf Filing Deadline: As defined in Section 2(a)(i) hereof.

Shelf Registration Statement: As defined in Section 2(a)(i) hereof.

Suspension Notice: As defined in Section 4(c) hereof.

Suspension Period: As defined in Section 4(b)(i) hereof.

TIA: Trust Indenture Act of 1939, as amended, and the rules and regulations of the Commission thereunder, in each case, as in effect on the date the Indenture is qualified under the TIA.

Transfer Restricted Securities: Each of the Notes and each of the shares of Common Stock or New Securities issued upon conversion of Notes until the earliest of, in the case of any such Notes or share(s) of Common Stock or New Securities:

(i) the date on which such Notes or such shares of Common Stock or New Securities issued upon conversion thereof has been effectively registered under the Securities Act and disposed of in accordance with the Shelf Registration Statement;

(ii) the date on which such Notes or such shares of Common Stock or New Securities issued upon conversion thereof is transferred in compliance with Rule 144 under the Securities Act or may be sold or transferred by a person who is not an affiliate of the Issuer pursuant to Rule 144 under the Securities Act (or any other similar provision then in force) without any volume or manner of sale restrictions thereunder; or

(iii) the date on which such Notes or such shares of Common Stock or New Securities issued upon conversion ceases to be outstanding (whether as a result of repurchase and cancellation, conversion or otherwise).

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Trustee means Wells Fargo Bank, N.A. as trustee.

Underwritten Registration or Underwritten Offering: A registration in which Notes of the Issuer are sold to an underwriter for reoffering to the public pursuant to the Shelf Registration Statement.

2. **Shelf Registration.**

(a) The Issuer shall:

(i) not later than 90 days after the date hereof (the “**Shelf Filing Deadline**”), cause to be filed a registration statement for an offering to be made on a continuous basis pursuant to Rule 415 under the Securities Act (together with any amendments thereto and including any documents incorporated by reference therein, the “**Shelf Registration Statement**”), which Shelf Registration Statement shall provide for resales of all Transfer Restricted Securities held by Holders that have provided the information required pursuant to the terms of Section 2(b) hereof;

(ii) use reasonable best efforts to cause the Shelf Registration Statement to be declared effective by the Commission not later than 180 days after the date hereof (the “**Effectiveness Target Date**”); and

(iii) use reasonable best efforts to keep the Shelf Registration Statement continuously effective, supplemented and amended as required by, and subject to, the provisions of Section 4(b) hereof to the extent necessary to ensure that it (A) is available for resales by the Holders of Transfer Restricted Securities entitled to the benefit of this Agreement and (B) conforms with the requirements of this Agreement and the Securities Act for a period (the “**Effectiveness Period**”) ending on the earliest of:

(1) the date when the Holders of the Transfer Restricted Securities are able to sell under Rule 144(k) under the Securities Act all Transfer Restricted Securities immediately without volume, manner of sale, filing or other restriction; or

(2) the date when all Transfer Restricted Securities are registered under the Shelf Registration Statement and sold pursuant thereto; or

(3) the date when all Transfer Restricted Securities have ceased to be outstanding (whether as a result of repurchase and cancellation, conversion or otherwise).

(b) To have its Transfer Restricted Securities included in the Shelf Registration Statement pursuant to this Agreement, each Holder shall complete the Selling

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Securityholder Notice and Questionnaire, the form of which is contained in Annex A to the Offering Memorandum relating to the Notes (the “**Questionnaire**”). The Issuer shall mail the Questionnaire to each Holder identified in the records of the Depository Trust Company not less than 20 Business Days (but not more than 40 Business Days) prior to the time the Issuer intends in good faith to have the Shelf Registration Statement declared effective by the Commission. Holders are required to complete and deliver the Questionnaire to the Issuer within 10 Business Days prior to the effectiveness of the Registration Statement (the “**Questionnaire Deadline**”) in order to be named as selling securityholders in the Prospectus at the time that the Shelf Registration Statement is declared effective. Upon receipt of a completed Questionnaire from a Holder on or prior to the Questionnaire Deadline, the Issuer shall include such Holder’s Transfer Restricted Securities in the Shelf Registration Statement and the Prospectus. In addition, promptly upon the request of a Holder given to the Issuer at any time, the Issuer shall deliver a Questionnaire to such Holder. With respect to any Holder that does not fully complete and deliver a Questionnaire prior to the Questionnaire Deadline, Issuer will not be required to name such Holder as a selling securityholder in the Shelf

Registration Statement at the time that it is declared effective. Upon receipt of a completed Questionnaire from a Holder who did not complete and deliver a Questionnaire prior to the Questionnaire Deadline, the Issuer shall, within 30 Business Days of such receipt, file such amendments to the Shelf Registration Statement or supplements to a related Prospectus as are necessary to permit such Holder to deliver such Prospectus to transferees of Transfer Restricted Securities; provided, that the Issuer shall not be obligated to file more than one amendment or supplement for all such Holders in any one fiscal quarter.

The Issuer will give notice of the effectiveness of the Shelf Registration Statement to all Holders who have properly delivered to the Issuer completed Questionnaires as described above either (i) by electronic mail at the applicable email address; or (ii) in writing at the applicable mailing address, in each case, as set forth in each such Holder's Questionnaire. The Issuer will have no obligation to provide notice of the effectiveness of the Shelf Registration Statement to any Holder who delivers a Questionnaire after the effectiveness notice described above has been delivered.

(c) Upon receipt of written request for additional information from the Issuer, each Holder who intends to be named as a selling securityholder in the Shelf Registration Statement shall furnish to the Issuer in writing, within 10 Business Days after such Holder's receipt of such request, such additional information regarding such Holder and the proposed distribution by such Holder of its Transfer Restricted Securities, in connection with the Shelf Registration Statement or Prospectus or preliminary Prospectus included therein and in any application to be filed with or under state securities law, as the Issuer may reasonably request. In connection with all such requests for information from Holders of Transfer Restricted Securities, the Issuer shall notify such Holders of the requirements set forth in this paragraph regarding their obligation to provide the information requested pursuant to this Section 2. Each Holder as to which the Shelf Registration Statement is being effected agrees to furnish promptly to the Issuer all information required to be disclosed in order to make information previously furnished to the Issuer by such Holder not materially misleading.

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3. *Additional Interest.*

(a) If:

(i) the Shelf Registration Statement is not filed with the Commission prior to or on the Shelf Filing Deadline;

(ii) the Shelf Registration Statement has not been declared effective by the Commission prior to or on the Effectiveness Target Date;

(iii) except as provided in Section 4(b)(i) hereof, the Shelf Registration Statement is filed and declared effective but, during the Effectiveness Period, shall thereafter cease to be effective or fail to be usable for its intended purpose without being succeeded within five Business Days by a post-effective amendment to the Shelf Registration Statement, a supplement to the Prospectus or a report filed with the Commission pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act that cures such failure and, in the case of a post-effective amendment, is itself immediately declared effective; or

(iv) (A) prior to or on the 45th or 60th day, as the case may be, of any Suspension Period, such suspension has not been terminated or (B) Suspension Periods exceed an aggregate of 90 days in any 360 day period,

(each such event referred to in foregoing clauses (i) through (iv), a "**Registration Default**"), the Issuer hereby agrees to pay additional interest ("**Additional Interest**") with respect to the Transfer Restricted Securities from and including the day following the Registration Default to but excluding the day on which the Registration Default has been cured, accruing at a rate, to each holder of Notes, (x) with respect to the first 90-day period during which a Registration Default shall have occurred and be continuing, equal to 0.25% per annum of the principal amount of the Notes, and (y) with respect to the period commencing on the 91st day following the day the Registration Default shall have occurred and be continuing, equal to 0.50% per annum of the principal amount of the Notes; provided that in no event shall Additional Interest accrue at an aggregate rate per year exceeding 0.50% of the principal amount of the Notes; provided further that in no event shall Additional Interest plus any Special Interest (as defined in the Indenture) accrue at an aggregate rate per year exceeding 0.50% of the principal amount of the Notes. No Additional Interest shall be payable on any Notes that have been converted into shares of Common Stock.

(b) All accrued Additional Interest shall be paid in arrears to Record Holders by the Issuer on each Additional Interest Payment Date by wire transfer of immediately available funds or by federal funds check and in accordance with the terms of the Indenture. Following the cure of all Registration Defaults relating to the Notes, the accrual of Additional Interest with respect to such Notes will cease. The Issuer agrees to deliver all notices, certificates and other documents contemplated by the Indenture in connection with the payment of Additional Interest.

If a Transfer Restricted Security ceases to be a Transfer Restricted Security, such cessation will not relieve the issuer from any liability under this Section 3 that was accrued but unpaid immediately prior to such cessation. The Additional Interest set forth above shall be the

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exclusive monetary remedy available to the Holders of Transfer Restricted Securities for such Registration Default.

4. *Registration Procedures.*

(a) In connection with the registration of the Transfer Restricted Securities, the Issuer shall comply with all the provisions of Section 4(b) hereof and shall use its reasonable best efforts to effect such registration to permit the sale of the Transfer Restricted Securities being sold in accordance with the intended method or methods of distribution thereof, and pursuant thereto, shall as expeditiously as possible prepare and file with the Commission a Shelf Registration Statement relating to the registration on any appropriate form under the Securities Act.

(b) In connection with the Shelf Registration Statement and any Prospectus required by this Agreement to permit the sale or resale of Transfer Restricted Securities, the Issuer shall:

(i) Subject to any notice by the Issuer in accordance with this Section 4(b) of the existence of any fact or event of the kind described in Section 4(b)(iii)(D), use its reasonable best efforts to keep the Shelf Registration Statement continuously effective during the Effectiveness Period; upon the occurrence of any event that would cause the Shelf Registration Statement or the Prospectus contained therein (A) to contain a material misstatement or omission or (B) not be effective and usable for resale of Transfer Restricted Securities during the Effectiveness Period, the Issuer shall file promptly an appropriate amendment to the Shelf Registration Statement, a supplement to the Prospectus or a report filed with the Commission pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act, in the case of clause (A), correcting any such misstatement or omission, and, in the case of either clause (A) or (B), use its reasonable best efforts to cause such amendment to be declared effective and the Shelf Registration Statement and the related Prospectus to become usable for their intended purposes as soon as practicable thereafter. Notwithstanding the foregoing, the Issuer may suspend the effectiveness of the Shelf Registration Statement by written notice to the Holders for a period not to exceed an aggregate of 45 days in any 90-day period (each such period, a “**Suspension Period**”) and not to exceed an aggregate of 90 days in any 360-day period if:

(x) an event occurs and is continuing as a result of which the Shelf Registration Statement would, in the Issuer’s reasonable judgment, contain an untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein not misleading; and

(y) the Issuer reasonably determines that the disclosure of such event at such time would have a material adverse effect on the business of the Issuer (and its subsidiaries, if any, taken as a whole);

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provided that in the event the disclosure relates to a previously undisclosed proposed or pending material business transaction, the disclosure of which would impede the Issuer’s ability to consummate such transaction, the Issuer may extend a Suspension Period from 45 days to 60 days in any 90-day period.

(ii) Prepare and file with the Commission such amendments and post-effective amendments to the Shelf Registration Statement as may be necessary to keep the Shelf Registration Statement effective during the Effectiveness Period; 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, and to comply with the applicable provisions of Rules 424 and 430A under the Securities Act in a timely manner; and comply with the provisions of the Securities Act with respect to the disposition of all securities covered by the Shelf Registration Statement during the applicable period in accordance with the intended method or methods of distribution by the sellers thereof set forth in the Shelf Registration Statement or supplement to the Prospectus; provided, however, that in no event will such method(s) of distribution take the form of an Underwritten Offering without the prior written agreement of the Issuer.

(iii) Advise the underwriter(s), if any, and selling Holders promptly (but in any event within five Business Days of becoming aware of such event) and, if requested by such Persons, to confirm such advice in writing:

(A) when the Prospectus or any Prospectus supplement or post-effective amendment has been filed, and, with respect to the Shelf Registration Statement or any post-effective amendment thereto, when the same has become effective,

(B) of any request by the Commission for amendments to the Shelf Registration Statement or amendments or supplements to the Prospectus or for additional information relating thereto,

(C) of the issuance by the Commission of any stop order suspending the effectiveness of the Shelf Registration Statement under the Securities Act or of the suspension by any state securities commission of the qualification of the Transfer Restricted Securities for offering or sale in any jurisdiction, or the initiation of any proceeding for any of the preceding purposes, or

(D) of the existence of any fact or the happening of any event, during the Effectiveness Period, that makes any statement of a material fact made in the Shelf Registration Statement, the Prospectus, any amendment or supplement thereto, or any document incorporated by reference therein untrue, or that requires the making of any additions to or changes in the Shelf Registration Statement or the Prospectus in order to make the statements therein not misleading.

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If at any time the Commission shall issue any stop order suspending the effectiveness of the Shelf Registration Statement, or any state securities commission or other regulatory authority shall issue an order suspending the qualification or exemption from qualification of the Transfer Restricted Securities under state securities or Blue Sky laws, the Issuer shall use its reasonable best efforts to obtain the withdrawal or lifting of such order at the earliest possible time and will provide to the Initial Purchasers and each Holder who is named in the Shelf Registration Statement prompt notice of the withdrawal of any such order.

(iv) Furnish to one counsel for the selling Holders and each of the underwriter(s), if any, before filing with the Commission, a copy of the Shelf Registration Statement and copies of any Prospectus included therein or any amendments or supplements to the Shelf Registration Statement or Prospectus (other than documents incorporated by reference after the initial filing of the Shelf Registration Statement or any amendments or supplements the sole purpose of which is to name additional selling Holders), which documents will be subject to the review of such counsel and underwriter(s), if any, for a period of at least two Business Days but no more than five Business Days (in the case of the Shelf Registration Statement and Prospectus) and no more than two Business Days (in the case of any such amendment or supplement thereto), and the Issuer will not file the Shelf Registration Statement or Prospectus or any amendment or supplement to the Shelf Registration Statement or Prospectus (other than documents incorporated by reference after the initial filing of the

Shelf Registration Statement or any amendments or supplements the sole purpose of which is to name additional selling Holders) to which such counsel or the underwriter(s), if any, shall reasonably object prior to the filing thereof; provided, however, that such objection is provided in writing and specifies in reasonable detail the reason for such objection.

(v) In connection with an Underwritten Offering of the Transfer Restricted Securities pursuant to the Shelf Registration Statement, make available at reasonable times for inspection by one or more representatives of the selling Holders, designated in writing by a Majority of Holders whose Transfer Restricted Securities are included in the Shelf Registration Statement, any underwriter participating in any distribution pursuant to the Shelf Registration Statement, and any attorney or accountant retained by such selling Holders or any of the underwriter(s), all financial and other records, pertinent corporate documents and properties of the Issuer as shall be reasonably necessary to enable them to exercise any applicable due diligence responsibilities, and cause the officers, directors, managers and employees of the Issuer to supply all information reasonably requested by any such representative or representatives of the selling Holders, underwriter, attorney or accountant in connection with the Shelf Registration Statement after the filing thereof and before its effectiveness, provided, however, that any information designated by the Issuer as confidential at the time of delivery of such information shall be kept confidential by the recipient thereof and shall be subject, upon request of the Issuer, to the execution

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by such persons of a confidentiality agreement in a form that is reasonable in the context of a registered public offering.

(vi) If requested by any selling Holders or the underwriter(s), if any, promptly incorporate in the Shelf Registration Statement or Prospectus, pursuant to a supplement or post-effective amendment if necessary, such information as such selling Holders and underwriter(s), if any, may reasonably request to have included therein, including, without limitation: (1) information relating to the "Plan of Distribution" of the Transfer Restricted Securities, (2) information with respect to the principal amount of the Notes or number of shares of Common Stock being sold to such underwriter(s), (3) the purchase price being paid therefor and (4) any other terms of the offering of the Transfer Restricted Securities to be sold in such offering; and make all required filings of such Prospectus supplement or post-effective amendment as soon as reasonably practicable after the Issuer is notified of the matters to be incorporated in such Prospectus supplement or post-effective amendment.

(vii) Furnish to each selling Holder and each underwriter, if any, upon their request, without charge, at least one copy of the Shelf Registration Statement, as first filed with the Commission, and of each amendment thereto (and any documents incorporated by reference therein or exhibits thereto (or exhibits incorporated in such exhibits by reference) as such Person may request).

(viii) Deliver to each selling Holder and each of the underwriter(s), if any, without charge, as many copies of the Prospectus (including each preliminary prospectus) and any amendment or supplement thereto as such Persons reasonably may request; subject to any notice by the Issuer in accordance with this Section 4(b) of the existence of any fact or event of the kind described in Section 4(b)(iii)(D), the Issuer hereby consents to the use (in accordance with applicable law) of the Prospectus and any amendment or supplement thereto by each of the selling Holders and each of the underwriter(s), if any, in connection with the offering and the sale of the Transfer Restricted Securities covered by the Prospectus or any amendment or supplement thereto.

(ix) The Issuer shall:

(A) upon request, furnish to each selling Holder and each underwriter, if any, in such substance and scope as they may reasonably request and as are customarily made by issuers to underwriters in primary underwritten offerings for selling security holders, upon the date of closing of any sale of Transfer Restricted Securities in an Underwritten Registration:

(1) a certificate, dated the date of such closing, signed by the Chief Financial Officer or the Chief Executive Officer of the Issuer covering such matters as are customarily covered in closing certificates delivered to underwriters in connection with underwritten offerings of securities;

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(2) an opinion, dated the date of such closing, of counsel to the Issuer covering such of the matters as are customarily covered in legal opinions to underwriters in connection with underwritten offerings of securities; and

(3) a customary comfort letter, dated the date of such closing, from the independent public accountant of the Issuer (and from any other accountants whose report is contained or incorporated by reference in the Shelf Registration Statement) in the customary form and covering matters of the type customarily covered in comfort letters to underwriters in connection with underwritten offerings of securities;

(B) set forth in full in the underwriting agreement, if any, indemnification provisions and procedures which provide rights no less protective than those set forth in Section 6 hereof with respect to all parties to be indemnified; and

(C) deliver such other documents and certificates as may be reasonably requested by such parties to evidence compliance with clause (A) above and with any customary conditions contained in the underwriting agreement or other agreement entered into by the selling Holders pursuant to this clause (ix).

(x) Before any public offering of Transfer Restricted Securities, cooperate with the selling Holders, the underwriter(s), if any, and their respective counsel in connection with the registration and qualification of the Transfer Restricted Securities under the securities or Blue Sky laws of such jurisdictions in the United States as the selling Holders or underwriter(s), if any, may reasonably request

and do any and all other acts or things necessary or advisable to enable the disposition in such jurisdictions of the Transfer Restricted Securities covered by the Shelf Registration Statement; provided, however, that the Issuer shall not be required (A) to register or qualify as a foreign corporation or a dealer of securities where it is not now so qualified or to take any action that would subject it to the service of process in any jurisdiction where it is not now so subject or (B) to subject itself to taxation in any such jurisdiction if it is not now so subject.

(xi) Unless recorded in book-entry form, cooperate with the selling Holders and the underwriter(s), if any, to facilitate the timely preparation and delivery of certificates representing Transfer Restricted Securities to be sold and not bearing any restrictive legends (unless required by applicable securities laws); and enable such Transfer Restricted Securities to be in such denominations and registered in such names as the Holders or the underwriter(s), if any, may request at least two Business Days before any sale of Transfer Restricted Securities made by such underwriter(s); provided however, such selling Holders and the underwriter(s), if any, provide issuer with a certificate containing representations, warranties and covenants that are reasonable and customary in connection with such transactions.

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(xii) Use its reasonable best efforts to cause the Transfer Restricted Securities covered by the Shelf Registration Statement to be registered with or approved by such other U.S. governmental agencies or authorities as may be necessary to enable the seller or sellers thereof or the underwriter(s), if any, to consummate the disposition of such Transfer Restricted Securities.

(xiii) Subject to Section 4(b)(i) hereof, if any fact or event contemplated by Section 4(b)(iii)(D) hereof shall exist or have occurred, use its reasonable best efforts to prepare a supplement or post-effective amendment to the Shelf Registration Statement or related Prospectus or any document incorporated therein by reference or file any other reasonably required document so that, as thereafter delivered to the purchasers of Transfer Restricted Securities, the Prospectus will not contain an untrue statement of a material fact or omit to state 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.

(xiv) Provide CUSIP numbers for all Transfer Restricted Securities not later than the effective date of the Shelf Registration Statement and provide the Trustee under the Indenture with certificates for the Notes that are in a form eligible for deposit with The Depository Trust Company.

(xv) Cooperate and assist in any filings required to be made with the NASD and in the performance of any due diligence investigation by any underwriter that is required to be retained in accordance with the rules and regulations of the NASD.

(xvi) Otherwise use its reasonable best efforts to comply with all applicable rules and regulations of the Commission and all reporting requirements under the Exchange Act.

(xvii) Cause the Indenture to be qualified under the TIA not later than the effective date of the Shelf Registration Statement required by this Agreement, and, in connection therewith, cooperate with the Trustee and the holders of the Notes to effect such changes to the Indenture as may be required for such Indenture to be so qualified in accordance with the terms of the TIA; and execute and use its commercially reasonable efforts to cause the Trustee thereunder to execute all documents that may be required by Trustee to effect such changes and all other forms and documents required to be filed with the Commission to enable such Indenture to be so qualified in a timely manner.

(xviii) Cause all Transfer Restricted Securities covered by the Shelf Registration Statement to be listed or quoted, as the case may be, on each securities exchange or automated quotation system on which similar securities issued by the Issuer are then listed or quoted.

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(xix) Provide to each Holder upon written request each document filed with the Commission pursuant to the requirements of Section 13 and Section 15 of the Exchange Act after the effective date of the Shelf Registration Statement.

(xx) If requested in writing in connection with a disposition of Transfer Restricted Securities pursuant to a Registration Statement, make reasonably available for inspection during normal business hours by a representative for the Holders of such Transfer Restricted Securities and any Broker-Dealers, attorneys and accountants retained by such Holders, all relevant financial and other records and pertinent corporate documents and properties of the Issuer and its subsidiaries, and cause the appropriate officers, directors and employees of the Issuer and its subsidiaries to make reasonably available for inspection during normal business hours on reasonable notice all relevant information reasonably requested by such representative for the Holders or any such Broker-Dealers, attorneys or accountants in connection with such disposition, in each case as is customary for similar "due diligence" examinations; provided, however, that such persons shall first agree in writing with the Issuer that any information that is reasonably and in good faith designated by the Issuer in writing as confidential at the time of delivery of such information shall be kept confidential by such persons and shall be used solely for the purposes of exercising rights under this Agreement, unless (i) disclosure of such information is required by court or administrative order or is necessary to respond to inquiries of regulatory authorities, (ii) disclosure of such information is required by law (including any disclosure requirements pursuant to federal securities laws in connection with the filing of any Shelf Registration Statement or the use of any Prospectus referred to in this Agreement), (iii) such information becomes generally available to the public other than as a result of a disclosure or failure to safeguard by any such person or (iv) such information becomes available to any such person from a source other than the Issuer and such source is not bound by a confidentiality agreement, and provided, that the foregoing inspection and information gathering shall, to the greatest extent possible, be coordinated on behalf of all the Holders and the other parties entitled thereto by the

counsel referred to in Section 5 and provided further, that the Issuer shall not be required to disclose any information subject to the attorney-client or attorney work product privilege if and to the extent such disclosure would constitute a waiver of such privilege.

(xxi) Use all reasonable efforts to comply with all applicable rules and regulations of the SEC.

(xxii) Make generally available to its securityholders earning statements (which need not be audited) satisfying the provisions of Section 11(a) of the Securities Act and Rule 158 thereunder (or any similar rule promulgated under the Securities Act) no later than 40 days after the end of any 3-month period (or 75 days after the end of any 12-month period if such period is a fiscal year) commencing on the first day of the first fiscal quarter of the Issuer commencing after the effective date of a Registration Statement, which statements shall cover said periods; provided, however, that such requirement shall be deemed satisfied

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if the Issuer timely files its periodic reports on Form 10-Q and Form 10-K (as applicable) pursuant to Section 13 or 15(d) of the Exchange Act.

(c) Each Holder agrees by acquisition of a Transfer Restricted Security that, upon receipt of any notice (a “**Suspension Notice**”) from the Issuer of the existence of any fact of the kind described in Section 4(b)(iii)(D) hereof, such Holder will, and will use its reasonable best efforts to cause any underwriter(s) in an Underwritten Offering to, forthwith discontinue disposition of Transfer Restricted Securities pursuant to the Shelf Registration Statement until:

(i) such Holder has received copies of the supplemented or amended Prospectus contemplated by Section 4(b)(xiii) hereof;
or

(ii) such Holder is advised in writing by the Issuer that the use of the Prospectus may be resumed, and has received copies of any additional or supplemental filings that are incorporated by reference in the Prospectus.

If so directed by the Issuer, each Holder will deliver to the Issuer (at the Issuer’s expense) all copies, other than permanent file copies then in such Holder’s possession, of the Prospectus covering such Transfer Restricted Securities that was current at the time of receipt of such notice of suspension.

5. **Registration Expenses.**

(a) All expenses incident to the performance of or compliance with this Agreement by the Issuer shall be borne by the Issuer regardless of whether a Shelf Registration Statement becomes effective, including, without limitation:

(i) all registration and filing fees and expenses (including filings made by the Initial Purchasers or any Holders with the NASD);

(ii) all fees and expenses of compliance with federal securities and state Blue Sky or securities laws;

(iii) all expenses of printing (including printing of Prospectuses and certificates for the Common Stock to be issued upon conversion of the Notes) and the expenses of the Issuer for messenger and delivery services and telephone;

(iv) all fees and disbursements of counsel to the Issuer and, subject to Section 5(b) below, the Holders of Transfer Restricted Securities;

(v) all application and filing fees in connection with listing (or authorizing for quotation) the Common Stock on a national securities exchange or automated quotation system pursuant to the requirements hereof; and

(vi) all fees and disbursements of the independent certified public accountant of the Issuer (including the expenses of any special audit and comfort letters required by or incident to such performance).

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The Issuer shall bear its internal expenses (including, without limitation, all salaries and expenses of their officers and employees performing legal, accounting or other duties), the expenses of any annual audit and the fees and expenses of any Person, including special experts, retained by the Issuer.

(b) In connection with the Shelf Registration Statement required by this Agreement, including any amendment or supplement thereto, and any other documents delivered to any Holders, the Issuer shall reimburse the Initial Purchasers and the Holders of Transfer Restricted Securities being registered pursuant to the Shelf Registration Statement, as applicable, for the reasonable fees and disbursements of not more than one counsel as may be chosen by a Majority of Holders for whose benefit the Shelf Registration Statement is being prepared, not to exceed an aggregate of \$20,000. The Issuer shall not be required to pay any underwriting discount, commission or similar fee related to the sale of any securities.

6. **Indemnification and Contribution.**

(a) The Issuer shall indemnify and hold harmless each Holder, such Holder’s officers, directors, partners and employees and each person, if any, who controls such Holder within the meaning of the Securities Act (each, an “**Indemnified Holder**”), from and against any loss, claim, damage or liability, joint or several, or any action in respect thereof (including, but not limited to, any loss, claim, damage, liability or action relating to

resales of the Transfer Restricted Securities), to which such Indemnified Holder may become subject, insofar as any such loss, claim, damage, liability or action arises out of, or is based upon (i) any untrue statement or alleged untrue statement of a material fact contained in the Shelf Registration Statement or Prospectus or any amendment or supplement thereto or (ii) the omission or alleged omission to state therein any material fact required to be stated therein or necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading, and shall reimburse each Indemnified Holder promptly upon demand for any legal or other expenses reasonably incurred by such Indemnified Holder in connection with investigating or defending or preparing to defend against any such loss, claim, damage, liability or action as such expenses are incurred; provided, however, that the Issuer shall not be liable in any such case to the extent that any such loss, claim, damage, liability or action arises out of, or is based upon, any untrue statement or alleged untrue statement or omission or alleged omission made in the Shelf Registration Statement or Prospectus or amendment or supplement thereto in reliance upon and in conformity with written information furnished to the Issuer by or on behalf of such Holder; provided, further, that the Issuer shall not be liable for any loss, liability, claim, damage or expense to the extent that it arises from a sale of Transfer Restricted Securities occurring during a Suspension Period, provided that Issuer shall have provided such Holder a Suspension Notice with respect to such Suspension Period prior to such sale.

(b) Each Holder, severally and not jointly, shall indemnify and hold harmless the Issuer, their officers, directors and employees and each person, if any, who controls the Issuer within the meaning of the Securities Act, from and against any loss, claim, damage or liability, joint or several, or any action in respect thereof, to which the Issuer or any such officer, director, employee or controlling person may become subject, insofar as any such loss, claim, damage or liability or action arises out of, or is based upon (i) any untrue statement or alleged untrue statement of any material fact contained in the Shelf Registration Statement or Prospectus

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or any amendment or supplement thereto or (ii) the omission or the 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 under which they were made, not misleading, but in each case only to the extent that such untrue statement or alleged untrue statement or omission or alleged omission was made in reliance upon and in conformity with written information furnished to the Issuer by or on behalf of such Holder (or its related Indemnified Holder) specifically for use therein, and shall reimburse the Issuer and any such officer, director, employee or controlling person promptly upon demand for any legal or other expenses reasonably incurred by the Issuer or any such officer, director, employee or controlling person in connection with investigating or defending or preparing to defend against any such loss, claim, damage, liability or action as such expenses are incurred. The foregoing indemnity agreement is in addition to any liability that any Holder may otherwise have to the Issuer and any such officer, employee or controlling person.

(c) Promptly after receipt by an indemnified party under this Section 6 of notice of any claim or the commencement of any action, the indemnified party shall, if a claim in respect thereof is to be made against the indemnifying party under this Section 6, notify the indemnifying party in writing of the claim or the commencement of that action; provided, however, that the failure to notify the indemnifying party shall not relieve it from any liability which it may have under this Section 6 except to the extent it has been materially prejudiced by such failure and, provided, further, that the failure to notify the indemnifying party shall not relieve it from any liability which it may have to an indemnified party otherwise than under this Section 6. If any such claim or action shall be brought against an indemnified party, and it shall notify the indemnifying party thereof, the indemnifying party shall be entitled to participate therein and, to the extent that it wishes, jointly with any other similarly notified indemnifying party, to assume the defense thereof with counsel satisfactory to the indemnified party. After notice from the indemnifying party to the indemnified party of its election to assume the defense of such claim or action, the indemnifying party shall not be liable to the indemnified party under this Section 6 for any legal or other expenses subsequently incurred by the indemnified party in connection with the defense thereof other than reasonable costs of investigation; provided, however, that a Majority of Holders shall have the right to employ a single counsel to represent jointly a Majority of Holders and their respective officers, directors, partners, employees and controlling persons who may be subject to liability arising out of any claim in respect of which indemnity may be sought by a Majority of Holders against the Issuer under this Section 6, if a Majority of Holders seeking indemnification shall have been advised in good faith by legal counsel that there may be one or more legal defenses available to them and their respective officers, employees and controlling persons that are different from or additional to those available to the Issuer and its officers, directors, employees and controlling persons, the fees and expenses of a single separate counsel shall be paid by the Issuer. No indemnifying party shall:

(i) without the prior written consent of the indemnified parties (which consent shall not be unreasonably withheld) settle or compromise or consent to the entry of any judgment with respect to any pending or threatened claim, action, suit or proceeding in respect of which indemnification or contribution may be sought hereunder (whether or not the indemnified parties are actual or potential parties to such claim or action) unless such settlement, compromise or consent

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includes an unconditional release of each indemnified party from all liability arising out of such claim, action, suit or proceeding, or

(ii) be liable for any settlement of any such action effected without its written consent (which consent shall not be unreasonably withheld), but if settled with its written consent or if there be a final judgment for the plaintiff in any such action, the indemnifying party agrees to indemnify and hold harmless any indemnified party from and against any loss or liability by reason of such settlement or judgment.

(d) If the indemnification provided for in this Section 6 shall for any reason be unavailable or insufficient to hold harmless an indemnified party under Section 6(a) or 6(b) in respect of any loss, claim, damage or liability (or action in respect thereof) referred to therein, each 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 loss, claim, damage or liability (or action in respect thereof):

(i) in such proportion as is appropriate to reflect the relative benefits received by the Issuer from the offering and sale of the Transfer Restricted Securities on the one hand and a Holder with respect to the sale by such Holder of the Transfer Restricted Securities on the other, or

(ii) if the allocation provided by clause (6)(d)(i) is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause 6(d)(i) but also the relative fault of the Issuer on the one hand and the Holders on the other in connection with the statements or omissions or alleged statements or alleged omissions that resulted in such loss, claim, damage or liability (or action in respect thereof), as well as any other relevant equitable considerations.

The relative benefits received by the Issuer on the one hand and a Holder on the other with respect to such offering and such sale shall be deemed to be in the same proportion as the total net proceeds from the offering of the Notes purchased under the Purchase Agreement (net of discounts and commissions but before deducting expenses) received by the Issuer on the one hand, bear to the total proceeds received by such Holder with respect to its sale of Transfer Restricted Securities on the other. The relative fault of the parties shall be determined by reference to whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the Issuer on the one hand or the Holders on the other, the intent of the parties and their relative knowledge, access to information and opportunity to correct or prevent such statement or omission. The Issuer and each Holder agree that it would not be just and equitable if the amount of contribution pursuant to this Section 6(d) were determined by *pro rata* allocation or by any other method of allocation that does not take into account the equitable considerations referred to in the first sentence of this paragraph (d). The amount paid or payable by an indemnified party as a result of the loss, claim, damage or liability, or action in respect thereof, referred to above in this Section 6 shall be deemed to include, for purposes of this Section 6, any legal or other expenses reasonably incurred by such indemnified party in connection with investigating or defending or preparing to

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defend any such action or claim. Notwithstanding the provisions of this Section 6, no Holder shall be required to contribute any amount in excess of the amount by which the total price at which the Transfer Restricted Securities purchased by it were resold exceeds the amount of any damages which such Holder has otherwise been required to pay by reason of any untrue or alleged untrue statement or omission or alleged omission. 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. The Holders' obligations to contribute as provided in this Section 6(d) are several and not joint.

(e) The indemnity and contribution provisions contained in this Section 6 shall remain operative and in full force and effect regardless of (i) any termination of this Agreement, (ii) any investigation made by or on behalf of any Holder or any person controlling any Holder, or the Issuer, or the Issuer's officers or directors or any person controlling the Issuer and (iii) the sale of any Transfer Restricted Securities by any Holder.

7. **Rule 144A.** In the event the Issuer is not subject to Section 13 or 15(d) of the Exchange Act, the Issuer hereby agrees with each Holder, for so long as any Transfer Restricted Securities remain outstanding, to make available to any Holder or beneficial owner of Transfer Restricted Securities in connection with any sale thereof and any prospective purchaser of such Transfer Restricted Securities from such Holder or beneficial owner, the information required by Rule 144A(d)(4) under the Securities Act in order to permit resales of such Transfer Restricted Securities pursuant to Rule 144A.

8. **Participation in Underwritten Registrations.** No Holder may participate in any Underwritten Registration hereunder unless such Holder:

(i) agrees to sell such Holder's Transfer Restricted Securities on the basis provided in any underwriting arrangements approved by the Persons entitled hereunder to approve such arrangements; and

(ii) fully completes and executes all reasonable questionnaires, powers of attorney, indemnities, underwriting agreements, lock-up letters and other documents required under the terms of such underwriting arrangements.

9. **Selection of Underwriters.** The Holders of Transfer Restricted Securities covered by the Shelf Registration Statement who desire to do so may sell such Transfer Restricted Securities in an Underwritten Offering if approved by the Issuer, as provided in Section 4(b)(ii). In any such Underwritten Offering, the investment banker or investment bankers and manager or managers that will administer the offering will be selected by a Majority of Holders whose Transfer Restricted Securities are included in such offering; provided, that such investment bankers and managers must be reasonably satisfactory to the Issuer.

10. **Miscellaneous.**

(a) **Remedies.** The Issuer acknowledges and agrees that any failure by the Issuer to comply with its obligations under Section 2 hereof may result in material irreparable injury to the Initial Purchasers or the Holders for which there is no adequate remedy at law, that it will not be possible to measure damages for such injuries precisely and that, in the event of any

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such failure, the Initial Purchasers or any Holder may obtain such relief as may be required to specifically enforce the obligations of the Issuer under Section 2 hereof. The Issuer further agrees to waive the defense in any action for specific performance that a remedy at law would be adequate.

(b) **Adjustments Affecting Transfer Restricted Securities.** The Issuer shall not take any action with the primary purpose of adversely affecting the ability of the Holders of the Transfer Restricted Securities as a class to include such Transfer Restricted Securities in a registration undertaken pursuant to this Agreement.

(c) **No Inconsistent Agreements.** The Issuer will not, on or after the date of this Agreement, enter into any agreement with respect to its securities that is inconsistent with the rights granted to the Holders in this Agreement or otherwise conflicts with the provisions hereof. In addition, the Issuer shall not grant to any of its security holders (other than the Holders of Transfer Restricted Securities in such capacity) the right to include any securities in the Shelf Registration Statement provided for in this Agreement other than the Transfer Restricted Securities. Except as disclosed in the Offering

Memorandum, the Issuer has not previously entered into any agreement (which has not expired or been terminated) granting any registration rights with respect to its securities to any Person which rights conflict with the provisions hereof.

(d) **Amendments and Waivers.** Except as provided in the next paragraph, this Agreement may not be amended, modified or supplemented, and waivers or consents to or departures from the provisions hereof may not be given, unless the Issuer has obtained the written consent of a Majority of Holders or such greater percentage of the Holders as required by the Indenture.

In the event of a merger or consolidation or sale, assignment, conveyance, transfer, lease or other disposition of all or substantially all of the properties and assets of the Issuer and its subsidiaries on a consolidated basis, the Issuer shall procure the assumption of its obligations under this Agreement (which it is understood and agreed shall include the registration of any other securities into which the Notes or the Common Stock (the “**New Securities**”) have become convertible on substantially the same terms as provided for the registration of the Common Stock) by the Person (if other than the Issuer) formed by such consolidation or into which the Issuer is merged or the Person who acquires by sale, assignment, conveyance, transfer, lease or other disposition all or substantially all of the properties and assets of the Issuer and its subsidiaries on a consolidated basis and this Agreement may be amended, modified or supplemented without the consent of any Holders to provide for such assumption of the Issuer’s obligations hereunder (including the registration of any New Securities). Without the consent of each Holder of the Notes, no amendment or modification may change the provisions relating to the payment of Additional Interest during the pendency of a Registration Default.

Each Holder of Transfer Restricted Securities outstanding at the time of any amendment, modification, supplement, waiver or consent or thereafter shall be bound by any amendment, modification, supplement, waiver or consent effected pursuant to this Section 10(d), whether or not any notice, writing or marking indicating such amendment, modification, supplement, waiver or consent appears on the Transfer Restricted Securities or is delivered to such Holder.

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(e) **Notices.** All notices and other communications provided for or permitted hereunder shall be made in writing by hand-delivery, first-class mail (registered or certified, return receipt requested), telex, facsimile transmission, or air courier guaranteeing overnight delivery:

(i) if to a Holder, at the address set forth on the records of the registrar under the Indenture or the transfer agent of the Common Stock, as the case may be; and

(ii) if to the Issuer:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008

Attention: Executive Vice President
Telephone: (760) 931-9200
Facsimile: (760) 603-4650

With a copy to:

Attention: General Counsel
Telephone: (760) 931-9200
Facsimile: (760) 268-4922

All such notices and communications shall be deemed to have been duly given: (i) at the time delivered by hand, if personally delivered; (ii) five Business Days after being deposited in the mail, postage prepaid, if mailed; (iii) when answered back, if telexed; (iv) when receipt acknowledged, if transmitted by facsimile; and (v) on the next Business Day, if timely delivered to an air courier guaranteeing overnight delivery. In addition, (y) Issuer may provide notice to any Holder by sending an electronic mail to the email address specified on such Holder’s Questionnaire and (z) Issuer may satisfy its obligations to furnish, deliver, supply or make available any document under this Agreement by filing it on the Commission’s electronic data gathering and retrieval system (EDGAR).

(f) **Successors and Assigns.** This Agreement shall inure to the benefit of and be binding upon the successors and assigns of each of the parties, including without limitation and without the need for an express assignment, subsequent Holders of Transfer Restricted Securities; provided, however, that (i) this Agreement shall not inure to the benefit of or be binding upon a successor or assign of a Holder unless and to the extent such successor or assign acquired Transfer Restricted Securities from such Holder and (ii) nothing contained herein shall be deemed to permit any assignment, transfer or other disposition of Transfer Restricted Securities in violation of the terms of the Purchase Agreement or the Indenture. If any transferee of any Holder shall acquire Transfer Restricted Securities, in any manner, whether by operation of law or otherwise, such Transfer Restricted Securities shall be held subject to all of the terms of this Agreement, and by taking and holding such Transfer Restricted Securities such person shall

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be conclusively deemed to have agreed to be bound by and to perform all of the terms and provisions of this Agreement.

(g) **Counterparts.** This Agreement may be executed in any number of counterparts and by the parties hereto in separate counterparts, each of which when so executed shall be deemed to be an original and all of which taken together shall constitute one and the same agreement.

(h) **Notes Held by the Issuer or Its Affiliates.** Whenever the consent or approval of Holders of a specified percentage of Transfer Restricted Securities is required hereunder, Transfer Restricted Securities held by the Issuer or its “affiliates” (as such term is defined in Rule 405 under the

Securities Act) shall not be counted in determining whether such consent or approval was given by the Holders of such required percentage.

- (i) **Headings.** The headings in this Agreement are for convenience of reference only and shall not limit or otherwise affect the meaning hereof.
- (j) **Governing Law.** This Agreement shall be governed by, and construed in accordance with, the law of the State of New York.
- (k) **Severability.** If any one or more of the provisions contained herein, or the application thereof in any circumstance, is held invalid, illegal or unenforceable, the validity, legality and enforceability of any such provision in every other respect and of the remaining provisions contained herein shall not be affected or impaired thereby.
- (l) **Entire Agreement.** This Agreement is intended by the parties as a final expression of their agreement and intended to be a complete and exclusive statement of the agreement and understanding of the parties hereto in respect of the subject matter contained herein. There are no restrictions, promises, warranties or undertakings, other than those set forth or referred to herein with respect to the registration rights granted by the Issuer with respect to the Transfer Restricted Securities. This Agreement supersedes all prior agreements and understandings between the parties with respect to such subject matter.
- (m) **Termination.** This Agreement and the obligations of the parties hereunder shall terminate upon the end of the Effectiveness Period, except for any liabilities or obligations under Sections 5 or 6 hereof and the obligations to make payments of and provide for liquidated damages under Section 3 hereof to the extent such damages accrue prior to the end of the Effectiveness Period, each of which shall remain in effect in accordance with its terms.

[Signature page follows]

IN WITNESS WHEREOF, the parties have executed this Agreement as of the date first written above.

ISIS PHARMACEUTICALS, INC.

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

LEHMAN BROTHERS INC.

BY: LEHMAN BROTHERS INC.

By: /s/ Tran Nguyen
Authorized Representative

SCHEDULE I

Initial Purchasers

Lehman Brothers Inc.
Cowen and Company, LLC
Needham & Company, LLC
Leerink Swann & Co., Inc.

\$125,000,000

ISIS PHARMACEUTICALS, INC.

2⁵/₈% Convertible Subordinated Notes due 2027PURCHASE AGREEMENT

January 17, 2007

LEHMAN BROTHERS INC.,
 As Representative of the several
 Initial Purchasers named in Schedule I attached hereto,
 c/o Lehman Brothers Inc.
 745 Seventh Avenue
 New York, New York 10019

Ladies and Gentlemen:

Isis Pharmaceuticals, Inc., a Delaware corporation (the “**Company**”), proposes, upon the terms and conditions set forth in this agreement (this “**Agreement**”), to issue and sell to you, as the initial purchasers (the “**Initial Purchasers**”), \$125,000,000 in aggregate principal amount of its 2⁵/₈% Convertible Subordinated Notes due 2027 (the “**Firm Securities**”). The Firm Securities will (i) have terms and provisions that are summarized in the Pricing Disclosure Package (as defined below) and Offering Memorandum (as defined below) and (ii) are to be issued pursuant to an Indenture (the “**Indenture**”) to be entered into between the Company and Wells Fargo Bank, NA, as trustee (the “**Trustee**”). The Company also proposes to issue and sell to the Initial Purchasers not more than an additional \$37,500,000 principal amount of its 2⁵/₈% Convertible Subordinated Notes due 2027 (the “**Additional Securities**”) if and to the extent that you, as Representative of the Initial Purchasers, shall have determined to exercise, on behalf of the Initial Purchasers, the right to purchase such 2⁵/₈% Convertible Subordinated Notes due 2027 granted to the Initial Purchasers in Section 3(a) hereof. The Firm Securities and the Additional Securities are hereinafter collectively referred to as the “**Securities**.” The Securities will be convertible into shares of the Company’s common stock (par value \$0.001 per share) (the “**Underlying Securities**”). This is to confirm the agreement concerning the purchase of the Securities from the Company by the Initial Purchasers.

1. *Purchase and Resale of the Securities.* The Securities will be offered and sold to the Initial Purchasers without registration under the Securities Act of 1933, as amended (the “**Securities Act**”), in reliance on an exemption pursuant to Section 4(2) under the Securities Act. The Company has prepared a preliminary offering memorandum, dated January 16, 2007 (together with the documents incorporated by reference therein, the “**Preliminary Offering Memorandum**”), a pricing term sheet substantially in the form attached hereto as Schedule II (the “**Pricing Term Sheet**”) setting forth the terms of the Securities omitted from the Preliminary Offering Memorandum and an offering memorandum, dated January 17, 2007 (together with the documents incorporated by reference therein, the “**Offering Memorandum**”),

setting forth information regarding the Company and the Securities (as defined herein). The Preliminary Offering Memorandum, as supplemented and amended as of the Applicable Time (as defined below), together with the Pricing Term Sheet and any of the documents listed on Schedule III hereto are collectively referred to as the “**Pricing Disclosure Package**.” The Company hereby confirms that it has authorized the use of the Preliminary Offering Memorandum, the Pricing Disclosure Package and the Offering Memorandum in connection with the offering and resale of the Securities by the Initial Purchasers. “**Applicable Time**” means 7:00 p.m. (New York City time) on the date of this Agreement.

Any reference to the Preliminary Offering Memorandum, the Pricing Disclosure Package or the Offering Memorandum shall be deemed to refer to and include the Company’s most recent Annual Report on Form 10-K, the Company’s most recent Quarterly Report on Form 10-Q and all subsequent documents filed with the United States Securities and Exchange Commission (the “**Commission**”) pursuant to Section 13(a) or 15(d) of the United States Securities Exchange Act of 1934, as amended (the “**Exchange Act**”), on or prior to the date of the Preliminary Offering Memorandum, the Pricing Disclosure Package or the Offering Memorandum, as the case may be. Any reference to the Preliminary Offering Memorandum, Pricing Disclosure Package or the Offering Memorandum, as the case may be, as amended or supplemented, as of any specified date, shall be deemed to include (i) any documents filed with the Commission pursuant to Section 13(a) or 15(d) of the Exchange Act after the date of the Preliminary Offering Memorandum, Pricing Disclosure Package or the Offering Memorandum, as the case may be, and prior to such specified date. All documents referenced above that are filed under the Exchange Act and so deemed to be included in the Preliminary Offering Memorandum, Pricing Disclosure Package or the Offering Memorandum, as the case may be, or any amendment or supplement thereto are hereinafter called the “**Exchange Act Reports**.”

It is understood and acknowledged that upon original issuance thereof, and until such time as the same is no longer required under the applicable requirements of the Securities Act, the Securities (and all securities issued in exchange therefor or in substitution thereof) shall bear the following legend (along with such other legends as the Initial Purchasers and their counsel deem necessary):

“THE SECURITIES EVIDENCED HEREBY HAVE NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933, AS AMENDED (THE “SECURITIES ACT”) OR THE SECURITIES LAWS OF ANY STATE OR OTHER JURISDICTION. NEITHER THIS SECURITY NOR ANY INTEREST OR PARTICIPATION HEREIN MAY BE REOFFERED, SOLD, ASSIGNED, TRANSFERRED, PLEDGED, ENCUMBERED OR OTHERWISE DISPOSED OF IN THE ABSENCE OF SUCH REGISTRATION OR UNLESS THE TRANSACTION IS EXEMPT FROM, OR NOT SUBJECT TO, THE REGISTRATION REQUIREMENTS OF THE SECURITIES ACT. EACH PURCHASER OF THE SECURITY EVIDENCED HEREBY IS NOTIFIED THAT THE SELLER MAY BE RELYING ON THE EXEMPTION FROM SECTION 5 OF THE SECURITIES ACT PROVIDED BY RULE 144A THEREUNDER. THE HOLDER OF THIS SECURITY BY ITS ACCEPTANCE HEREOF (1) REPRESENTS THAT IT IS A “QUALIFIED INSTITUTIONAL BUYER” (AS DEFINED IN RULE 144A UNDER THE SECURITIES ACT),

(2) AGREES THAT IT WILL NOT PRIOR TO (X) THE DATE WHICH IS TWO YEARS (OR SUCH SHORTER PERIOD OF TIME AS PERMITTED BY RULE 144(K) UNDER THE SECURITIES ACT OR ANY SUCCESSOR PROVISION THEREUNDER) AFTER THE LATER OF THE ORIGINAL ISSUE DATE HEREOF (OR OF ANY PREDECESSOR OF THIS SECURITY) OR THE LAST DAY ON WHICH THE COMPANY OR ANY AFFILIATE OF THE COMPANY WAS THE OWNER OF THIS SECURITY (OR ANY PREDECESSOR OF THIS SECURITY) AND (Y) SUCH LATER DATE, IF ANY, AS MAY BE REQUIRED BY APPLICABLE LAW (THE "RESALE RESTRICTION TERMINATION DATE"), OFFER, SELL OR OTHERWISE TRANSFER THIS SECURITY EXCEPT (A) TO THE COMPANY, (B) PURSUANT TO A REGISTRATION STATEMENT WHICH HAS BEEN DECLARED EFFECTIVE UNDER THE SECURITIES ACT, (C) FOR SO LONG AS THE SECURITIES ARE ELIGIBLE FOR RESALE PURSUANT TO RULE 144A, TO A PERSON IT REASONABLY BELIEVES IS A "QUALIFIED INSTITUTIONAL BUYER" AS DEFINED IN RULE 144A UNDER THE SECURITIES ACT THAT PURCHASES FOR ITS OWN ACCOUNT OR FOR THE ACCOUNT OF A QUALIFIED INSTITUTIONAL BUYER TO WHOM NOTICE IS GIVEN THAT THE TRANSFER IS BEING MADE IN RELIANCE ON RULE 144A OR (D) PURSUANT TO ANY OTHER AVAILABLE EXEMPTION FROM THE REGISTRATION REQUIREMENTS OF THE SECURITIES ACT AND (3) AGREES THAT IT WILL GIVE TO EACH PERSON TO WHOM THIS SECURITY IS TRANSFERRED A NOTICE SUBSTANTIALLY TO THE EFFECT OF THIS LEGEND; PROVIDED THAT THE COMPANY, THE TRUSTEE AND THE REGISTRAR SHALL HAVE THE RIGHT PRIOR TO ANY SUCH OFFER, SALE OR TRANSFER PURSUANT TO CLAUSE (D) TO REQUIRE THE DELIVERY OF AN OPINION OF COUNSEL, CERTIFICATION AND/OR OTHER INFORMATION SATISFACTORY TO EACH OF THEM. THIS LEGEND WILL BE REMOVED UPON THE REQUEST OF THE HOLDER AFTER THE RESALE RESTRICTION TERMINATION DATE.

You have advised the Company that you will make offers (the "**Exempt Resales**") of the Securities purchased by you hereunder on the terms set forth in each of the Pricing Disclosure Package and the Offering Memorandum, as amended or supplemented, solely to persons (the "**Eligible Purchasers**") whom you reasonably believe to be "qualified institutional buyers" as defined in Rule 144A under the Securities Act ("**QIBs**"). You will offer the Securities to Eligible Purchasers initially at a price equal to 100% of the principal amount thereof plus accrued interest, if any. Such price may be changed at any time without notice.

Holders (including subsequent transferees) of the Securities will have the registration rights set forth in the registration rights agreement attached hereto as Exhibit A (the "**Registration Rights Agreement**") between the Company and the Initial Purchasers to be dated January 23, 2007 (the "**Closing Date**"), for so long as such Securities constitute "**Transfer Restricted Securities**" (as defined in the Registration Rights Agreement). Pursuant to the Registration Rights Agreement, the Company will agree to file with the Commission under the circumstances set forth therein, a shelf registration statement under the Securities Act (the

"**Resale Registration Statement**") relating to resales by holders of the Securities and the Underlying Securities.

2. *Representations, Warranties and Agreements of the Company.* The Company represents, warrants and agrees as follows:

(a) When the Securities are issued and delivered pursuant to this Agreement, the Securities will not be of the same class (within the meaning of Rule 144A under the Securities Act) as securities of the Company that are listed on a United States national securities exchange registered or that are quoted in a United States automated inter-dealer quotation system.

(b) Neither the Company nor any subsidiary is, and after giving effect to the offer and sale of the Securities and the application of the proceeds therefrom as described under "Use of Proceeds" in each of the Pricing Disclosure Package and the Offering Memorandum will be, (i) an "investment company" or a company "controlled" by an "investment company" within the meaning of the Investment Company Act of 1940 (the "**Investment Company Act**"), as amended, and the rules and regulations of the Commission thereunder or (ii) a "business development company" (as defined in Section 2(a)(48) of the Investment Company Act).

(c) Assuming that your representations and warranties in Section 3(b) are true, the purchase and resale of the Securities pursuant hereto (including pursuant to the Exempt Resales) is exempt from the registration requirements of the Securities Act. No form of general solicitation or general advertising within the meaning of Regulation D (including, but not limited to, advertisements, articles, notices or other communications published in any newspaper, magazine or similar medium or broadcast over television or radio, or any seminar or meeting whose attendees have been invited by any general solicitation or general advertising) was used by the Company or any of its representatives (other than you, as to whom the Company makes no representation) in connection with the offer and sale of the Securities.

(d) Each of the Preliminary Offering Memorandum, the Pricing Disclosure Package and the Offering Memorandum, each as of its respective date, contains all the information specified in, and meeting the requirements of, Rule 144A(d)(4) under the Securities Act.

(e) The Preliminary Offering Memorandum, the Pricing Disclosure Package and the Offering Memorandum have been prepared by the Company for use by the Initial Purchasers in connection with the Exempt Resales. No order or decree preventing the use of the Preliminary Offering Memorandum, the Pricing Disclosure Package or the Offering Memorandum, or any order asserting that the transactions contemplated by this Agreement are subject to the registration requirements of the Securities Act has been issued, and no proceeding for that purpose has commenced or is pending or, to the knowledge of the Company is contemplated.

(f) The Pricing Disclosure Package did not, as of the Applicable Time, and will not, as of the Closing Date, contain an untrue statement of a material fact or omit to state a material fact necessary in order to make the statements made therein, in the light of the

circumstances under which they were made, not misleading; *provided* that no representation or warranty is made as to information contained in or omitted from the Pricing Disclosure Package in reliance upon and in conformity with written information furnished to the Company through the Representative by or on behalf of any Initial Purchaser specifically for inclusion therein, which information is specified in Section 8(e).

(g) The Offering Memorandum will not, as of its date and as of the Closing Date, contain an untrue statement of a material fact or omit to state a material fact necessary in order to make the statements made therein, in the light of the circumstances under which they were made, not misleading; *provided* that no representation or warranty is made as to information contained in or omitted from the Offering Memorandum in reliance upon and in conformity with written information furnished to the Company through the Representative by or on behalf of any Initial Purchaser specifically for inclusion therein, which information is specified in Section 8(e).

(h) The Company has not made any offer to sell or solicitation of an offer to buy the Securities that would constitute a “free writing prospectus” (if the offering of the Securities was made pursuant to a registered offering under the Securities Act), as defined in Rule 405 under the Securities Act (a “**Free Writing Offering Document**”) without the prior consent of the Representative; any such Free Writing Offering Document the use of which has been previously consented to by the Initial Purchasers is set forth substantially in form and substance as attached hereto on Schedule III.

(i) The Exchange Act Reports, when they were or are filed with the Commission, conformed or will conform in all material respects to the applicable requirements of the Exchange Act and the applicable rules and regulations of the Commission thereunder. The Exchange Act Reports did not, when filed with the Commission, contain an untrue statement of material fact or omit to state a material fact necessary in order to make the statements made therein, in the light of the circumstances under which they were made, not misleading.

(j) The statistical and market-related data included under the captions “Business” in the Company’s annual report on Form 10-K for the year ended December 31, 2005 and in “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in the Company’s quarterly report on Form 10-Q for the nine months ended September 30, 2006 incorporated by reference in the Pricing Disclosure Package and the consolidated financial statements of the Company and its subsidiaries included in the Pricing Disclosure Package are based on or derived from sources that the Company believes do not contain an untrue statement of material fact or omit to state a material fact necessary in order to make the statements made therein, in light of the circumstances under which they were made, not misleading.

(k) Each of the Company and its subsidiaries (as defined in Section 15) has been duly organized and is validly existing and in good standing as a corporation or other business entity under the laws of its jurisdiction of organization and is duly qualified to do business and in good standing as a foreign corporation or other business entity in each jurisdiction in which its ownership or lease of property or the conduct of its businesses requires such qualification, except where the failure to be so qualified or in good standing would not, in

the aggregate, reasonably be expected to have a material adverse effect on the condition (financial or otherwise), results of operations, stockholders’ equity, properties, business or prospects of the Company and its subsidiaries taken as a whole or a material adverse effect on the performance by the Company of the performance of this Agreement, the Indenture, the Securities or the Registration Rights Agreement or the consummation of any of the transactions contemplated hereby or thereby (a “**Material Adverse Effect**”); each of the Company and its subsidiaries has all power and authority necessary to own or hold its properties and to conduct the businesses in which it is engaged. The Company does not own or control, directly or indirectly, any corporation, association or other entity other than (i) the subsidiaries listed in the Company’s Annual Report on Form 10-K for the most recent fiscal year and (ii) the Company’s Ibis Biosciences, Inc. subsidiary. None of the subsidiaries of the Company is a “significant subsidiary” (as defined in Rule 405 under the Securities Act).

(l) The Company has an authorized capitalization as set forth in each of the Pricing Disclosure Package and the Offering Memorandum on the dates indicated therein, and all of the issued shares of capital stock of the Company have been duly authorized and validly issued, are fully paid and non-assessable, conform to the description thereof contained in each of the Pricing Disclosure Package and the Offering Memorandum and were issued in compliance with federal and state securities laws and not in violation of any preemptive right, resale right, right of first refusal or similar right. All of the Company’s options, warrants and other rights to purchase or exchange any securities for shares of the Company’s capital stock have been duly authorized and validly issued, conform to the description thereof contained in each of the Pricing Disclosure Package and the Offering Memorandum and were issued in compliance with federal and state securities laws. There is no and has been no policy or practice of the Company to intentionally coordinate the grant of options to employees with the release or other public announcement of material information regarding the Company or its results of operations or prospects to minimize the exercise price of such options. All of the issued shares of capital stock of each subsidiary of the Company have been duly authorized and validly issued, are fully paid and non-assessable and are owned directly or indirectly by the Company, free and clear of all liens, encumbrances, equities or claims, except for such liens, encumbrances, equities or claims as would not, in the aggregate, reasonably be expected to have a Material Adverse Effect.

(m) The Company has all requisite corporate power and authority to execute, deliver and perform its obligations under the Indenture. The Indenture has been duly and validly authorized by the Company, and upon its execution and delivery and, assuming due authorization, execution and delivery by the Trustee, will constitute the valid and binding agreement of the Company, enforceable against the Company in accordance with its terms, except as such enforceability may be limited by bankruptcy, fraudulent conveyance, insolvency, reorganization, moratorium, and other laws relating to or affecting creditors’ rights generally and by general equitable principles (regardless of whether such enforceability is considered in a proceeding in equity or at law); no qualification of the Indenture under the Trust Indenture Act of 1939 (the “**1939 Act**”) is required in connection with the offer and sale of the Securities contemplated hereby or in connection with the Exempt Resales. The Indenture will conform in all material respects to the description thereof in each of the Pricing Disclosure Package and the Offering Memorandum.

(n) The Company has all requisite corporate power and authority to execute, issue, sell and perform its obligations under the Securities. The Securities have been duly authorized by the Company and, when duly executed by the Company in accordance with the terms of the Indenture, assuming due authentication of the Securities by the Trustee, upon delivery to the Initial Purchasers against payment therefor in accordance with the terms hereof, will be validly issued and delivered and will constitute valid and binding obligations of the Company entitled to the benefits of the Indenture, enforceable against the Company in accordance with their terms, except as such enforceability may be limited by bankruptcy, fraudulent conveyance, insolvency, reorganization, moratorium, and other laws relating to or affecting creditors' rights generally and by general equitable principles (regardless of whether such enforceability is considered in a proceeding in equity or at law). The Securities will conform in all material respects to the description thereof in each of the Pricing Disclosure Package and the Offering Memorandum.

(o) The Company has all the requisite corporate power and authority to issue the Underlying Securities issuable upon conversion of the Securities. The Underlying Securities have been duly and validly authorized by the Company and, when issued upon conversion of the Securities in accordance with the terms of the Securities, will be validly issued, fully paid and non-assessable, and the issuance of the Underlying Securities will not be subject to any preemptive or similar rights.

(p) The Company has all requisite corporate power and authority to execute, deliver and perform its obligations under the Registration Rights Agreement. The Registration Rights Agreement has been duly authorized by the Company and, when executed and delivered by the Company in accordance with the terms hereof and thereof, will be validly executed and delivered and (assuming the due authorization, execution and delivery thereof by you) will be the legally valid and binding obligation of the Company in accordance with the terms thereof, enforceable against the Company in accordance with its terms, except as such enforceability may be limited by bankruptcy, insolvency, reorganization, moratorium and other similar laws relating to or affecting creditor's rights generally, by general equitable principles (regardless of whether such enforceability is considered in a proceeding in equity or at law) and, as to rights of indemnification and contribution, by principles of public policy. The Registration Rights Agreement will conform in all material respects to the description thereof in each of the Pricing Disclosure Package and the Offering Memorandum.

(q) The Company has all requisite corporate power to execute, deliver and perform its obligations under this Agreement. This Agreement has been duly and validly authorized, executed and delivered by the Company.

(r) The issue and sale of the Securities, the execution, delivery and performance by the Company of the Securities, the Indenture, the Registration Rights Agreement and this Agreement, the application of the proceeds from the sale of the Securities as described under "Use of Proceeds" in each of the Pricing Disclosure Package and the Offering Memorandum and the consummation of the transactions contemplated hereby and thereby, will not (i) conflict with or result in a breach or violation of any of the terms or provisions of, impose any lien, charge or encumbrance upon any property or assets of the Company or its subsidiaries, or constitute a default under, any indenture, mortgage, deed of trust, loan agreement, license,

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lease or other agreement or instrument to which the Company or any of its subsidiaries is a party or by which the Company or any of its subsidiaries is bound or to which any of the property or assets of the Company or any of its subsidiaries is subject, (ii) result in any violation of the provisions of the charter or by-laws or similar organizational document of the Company or any of its subsidiaries or (iii) result in any violation of any statute or any judgment, order, decree, rule or regulation of any court or arbitrator or federal, state, local or foreign governmental agency or regulatory authority having jurisdiction over the properties or assets of the Company or any of its subsidiaries or any of their properties or assets ("**Governmental Authority**"), except, with respect to clauses (i) and (iii), conflicts, breaches or violations that would not reasonably be expected to have a Material Adverse Effect, and with respect to clause (i) those that have been waived or consented to prior to the execution of this Agreement.

(s) No consent, approval, authorization or order of, or filing, registration or qualification with any Governmental Authority is required for the issue and sale of the Securities, the execution, delivery and performance by the Company of the Securities, the Indenture, the Registration Rights Agreement and this Agreement, the application of the proceeds from the sale of the Securities as described under "Use of Proceeds" in each of the Pricing Disclosure Package and the Offering Memorandum and the consummation of the transactions contemplated hereby and thereby, except for the filing of a registration statement by the Company with the Commission pursuant to the Securities Act as required by the Registration Rights Agreement and such consents, approvals, authorizations, orders, filings, registrations or qualifications as may be required under state securities or Blue Sky laws in connection with the purchase and distribution of the Securities by the Initial Purchasers and listing of the Underlying Securities on the NASDAQ Global Market.

(t) Except as identified in the Pricing Disclosure Package and the Offering Memorandum, there are no contracts, agreements or understandings between the Company and any person granting such person the right to require the Company to file a registration statement under the Securities Act with respect to any securities of the Company (other than the Registration Rights Agreement) owned or to be owned by such person or to require the Company to include such securities in the securities registered pursuant to the Registration Rights Agreement or in any securities being registered pursuant to any other registration statement filed by the Company under the Securities Act.

(u) Neither the Company nor any other person acting on behalf of the Company has sold or issued any securities that would be integrated with the offering of the Securities contemplated by this Agreement pursuant to the Securities Act, the rules and regulations thereunder or the interpretations thereof by the Commission. The Company will take reasonable precautions designed to insure that any offer or sale, direct or indirect, in the United States or to any U.S. person (as defined in Rule 902 under the Securities Act), of any Securities or any substantially similar security issued by the Company, within six months subsequent to the date on which the distribution of the Securities has been completed (as notified to the Company by the Initial Purchasers), is made under restrictions and other circumstances reasonably designed not to affect the status of the offer and sale of the Securities in the United States and to U.S. persons contemplated by this Agreement as transactions exempt from the registration provisions of the Securities Act, including any sales pursuant to Rule 144A under the Securities Act.

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(v) Except as described in the each of the Pricing Disclosure Package and the Offering Memorandum, neither the Company nor any of its subsidiaries has sustained, since the date of the latest audited financial statements included in the Pricing Disclosure Package, any loss or interference with its business from fire, explosion, flood or other calamity, whether or not covered by insurance, or from any labor dispute or court or governmental action, order or decree, and, since such date, there has not been any change in the total current assets, capital stock or long-term debt of the Company or any of its subsidiaries or any adverse change, or any development involving a prospective adverse change, in or affecting the condition (financial or otherwise), results of operations, stockholders' equity, properties, management, business or prospects of the Company and its subsidiaries, taken as a whole, in each case except as would not, in the aggregate, reasonably be expected to have a Material Adverse Effect.

(w) The historical financial statements (including the related notes and supporting schedules) included or incorporated by reference in the Pricing Disclosure Package and the Offering Memorandum present fairly in all material respects the financial condition, results of operations and cash flows of the entities purported to be shown thereby, at the dates and for the periods indicated, and have been prepared in conformity with accounting principles generally accepted in the United States applied on a consistent basis throughout the periods involved. The other financial information and data included in the Offering Memorandum are, in all material respects, accurately presented and prepared on a basis consistent with such financial statements and the books and records of the Company.

(x) Ernst & Young LLP, who have certified certain financial statements of the Company, whose report appears in the Pricing Disclosure Package and who have delivered the initial letter referred to in Section 8(e) hereof, are independent public accountants as required by the Securities Act and the rules and regulations thereunder.

(y) (i) The Company and each of its subsidiaries has good and marketable title in fee simple to all real property and good and marketable title to all personal property owned by them, in each case free and clear of all liens, encumbrances and defects, except such as are described in the Pricing Disclosure Package and the Offering Memorandum and such as do not affect the value of such property and do not interfere with the use made and proposed to be made of such property by the Company or any of its subsidiaries; and (ii) all assets held under lease by the Company or any of its subsidiaries are held by them under valid, subsisting and enforceable leases, with such exceptions as do not interfere with the use made and proposed to be made of such assets by the Company or any of its subsidiaries; except, in the case of (i) and (ii), as would not, in the aggregate, reasonably be expected to have a Material Adverse Effect.

(z) Except such as are described in the Pricing Disclosure Package and the Offering Memorandum, the Company and each of its subsidiaries carry, or are covered by, insurance from insurers of recognized financial responsibility in such amounts and covering such risks as, based on the Company's internal assessments, is adequate for the conduct of their respective businesses and the value of their respective properties and as is customary for companies engaged in similar businesses in similar industries. All policies of insurance of the Company and its subsidiaries are in full force and effect; the Company and its subsidiaries are in compliance with the terms of such policies in all material respects; and neither the Company nor any of its subsidiaries has received notice from any insurer or agent of such insurer that capital

improvements or other expenditures are required or necessary to be made in order to continue such insurance; there are no claims by the Company or any of its subsidiaries under any such policy or instrument as to which any insurance company is denying liability or defending under a reservation of rights clause; and neither the Company nor any such subsidiary has any reason to believe that it will not be able to renew its existing insurance coverage as and when such coverage expires or to obtain similar coverage from similar insurers as may be necessary to continue its business at a cost that would not reasonably be expected to have a Material Adverse Effect.

(aa) The Company and each of its subsidiaries have such permits, licenses, patents, franchises, certificates of need and other approvals or authorizations of such Governmental Authorities ("**Permits**") as are necessary under applicable law to own their properties and conduct their businesses in the manner described in the Pricing Disclosure Package and the Offering Memorandum, except for any of the foregoing that would not, in the aggregate, reasonably be expected to have a Material Adverse Effect or except as described in the Pricing Disclosure Package and the Offering Memorandum; each of the Company and its subsidiaries has fulfilled and performed all of its obligations with respect to the Permits, and no event has occurred that allows, or after notice or lapse of time would allow, revocation or termination thereof or results in any other impairment of the rights of the holder or any such Permits, except for any of the foregoing that would not reasonably be expected to have a Material Adverse Effect or except as described in the Pricing Disclosure Package.

(bb) The Company and each of its subsidiaries own or possess adequate rights to use all patents, patent applications, inventions, trademarks, service marks, trade names, trademark registrations, service mark registrations, copyrights, licenses, know-how, software, systems and technology (including trade secrets and other unpatented and/or unpatentable proprietary or confidential information, systems or procedures) or other intellectual property, including, without limitation, all of the intellectual property described in the Pricing Disclosure Package and the Offering Memorandum as being owned or licensed by the Company and its subsidiaries (collectively, "**Intellectual Property**"), necessary for the conduct of their respective businesses, except where the failure to own or possess such Intellectual Property would not, individually or in the aggregate, have a Material Adverse Effect. The Company and its subsidiaries have no reason to believe that the conduct of their respective businesses will conflict with, and have not received any notice of any claim of conflict with, any such rights of others, except where such conflict or claims of conflict would not, individually or in the aggregate, have a Material Adverse Effect. Except as disclosed in the Pricing Disclosure Package and the Offering Memorandum, (A) there is no infringement, misappropriation or violation by third parties of any such Intellectual Property, except as such infringement, misappropriation or violation would not result in a Material Adverse Effect; (B) there is no pending or, to the knowledge of the Company and its subsidiaries, threatened action, suit, proceeding or claim by others challenging the rights of the Company and its subsidiaries in or to any such Intellectual Property, and the Company is unaware of any facts which would form a reasonable basis for any such claim which would have a Material Adverse Effect; (C) the Intellectual Property owned by the Company and its subsidiaries and, to the knowledge of the Company, the Intellectual Property licensed to the Company and its subsidiaries has not been adjudged invalid or unenforceable, in whole or in part, and there is no pending or threatened in writing action, suit, proceeding or claim by others challenging the validity or scope of any such Intellectual Property,

and the Company is unaware of any facts which would form a reasonable basis for any such claim which would have a Material Adverse Effect; (D) there is no pending or threatened action, suit, proceeding or claim by others that the Company or its subsidiaries infringe, misappropriate or otherwise violate any Intellectual Property or other proprietary rights of others, the Company and its subsidiaries have not received any written notice of such claim and the Company is unaware of any other facts which would form a reasonable basis for any such claim which would have a Material Adverse Effect; and (E) to the Company's knowledge, no employee of the Company or a subsidiary of the Company is in or has ever been in violation of any term of any employment contract, patent disclosure agreement, invention assignment agreement, non-competition agreement, non-solicitation agreement, nondisclosure agreement or any restrictive covenant to or with a former employer where the basis of such violation relates to such employee's employment with the Company or a subsidiary of the Company, or actions undertaken by the employee while employed with the Company or a subsidiary of the Company, except for such violations as would not have a Material Adverse Effect. To the Company's knowledge, all material technical information developed by and belonging to the Company and its subsidiaries which has not been patented has been kept confidential, except as would not have a Material Adverse Effect. The Company is not a party to or bound by any options, licenses or agreements with respect to the Intellectual Property that would be required to be described in a registration statement filed under the Securities Act or would be required to be filed as exhibits to a registration statement of the Company pursuant to Item 601(10) of Regulation S-K that have not been described or incorporated by reference in the Pricing Disclosure Package and the Offering Memorandum.

(cc) Except as described in the Pricing Disclosure Package and the Offering Memorandum, the Company and each of its subsidiaries: (A) are and at all times have been in full compliance with all statutes, rules, regulations, or guidances applicable to the ownership, testing, development, manufacture, packaging, processing, use, distribution, marketing, labeling, promotion, sale, offer for sale, storage, import, export or disposal of any product or product candidate manufactured or distributed by the Company and its subsidiaries ("**Applicable Laws**"); (B) have not received any U.S. Food and Drug Administration ("**FDA**") Form 483, notice of adverse finding, warning letter, untitled letter or other correspondence or notice from the FDA or any other Governmental Authority alleging or asserting noncompliance with any Applicable Laws or any licenses, certificates, approvals, clearances, authorizations, permits and supplements or amendments thereto required by any such Applicable Laws ("**Authorizations**"); (C) possess all Authorizations and such Authorizations are valid and in full force and effect and are not in violation of any term of any such Authorizations; (D) have not received written notice of any claim, action, suit, proceeding, hearing, enforcement, investigation, arbitration or other action from any Governmental Authority or third party alleging that any product operation or activity is in violation of any Applicable Laws or Authorizations and have no knowledge that any such Governmental Authority or third party is considering any such claim, litigation, arbitration, action, suit, investigation or proceeding; (E) have not received notice that any Governmental Authority has taken, is taking or intends to take action to limit, suspend, modify or revoke any Authorizations and have no knowledge that any such Governmental Authority is considering such action; (F) have filed, obtained, maintained or submitted all reports, documents, forms, notices, applications, records, claims, submissions and supplements or amendments as required by any Applicable Laws or Authorizations and represent that all such reports, documents, forms, notices, applications, records, claims, submissions and supplements or

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amendments were complete and correct on the date filed (or were corrected or supplemented by a subsequent submission), except where the failure to so file, obtain, maintain or submit would not reasonably be expected to have a Material Adverse Effect; and (G) have not, either voluntarily or involuntarily, initiated, conducted, or issued or caused to be initiated, conducted or issued, any recall, market withdrawal or replacement, safety alert, post-sale warning, "dear doctor" letter, or other notice or action relating to the alleged lack of safety or efficacy of any of its product or any alleged product defect or violation and, to the Company's knowledge, no third party has initiated, conducted or intends to initiate any such notice or action.

(dd) The studies, tests and preclinical and clinical trials conducted by or on behalf of the Company and each of its subsidiaries were and, if still pending, are being conducted in accordance with experimental protocols, procedures and controls pursuant to accepted professional scientific standards and all Applicable Laws and Authorizations, including, without limitation, the Federal Food, Drug and Cosmetic Act and the rules and regulations promulgated thereunder; the descriptions of the results of such studies, tests and trials contained in the Pricing Disclosure Package and the Offering Memorandum are accurate and complete in all material respects and fairly present the data derived from such studies, tests and trials; except to the extent disclosed in the Pricing Disclosure Package and the Offering Memorandum, the Company is not aware of any studies, tests or trials, the results of which the Company believes reasonably refute the study, test, or trial results described or referred to in the Pricing Disclosure Package and the Offering Memorandum when viewed in the context in which such results are described and the clinical state of development; and the Company and its subsidiaries have not received any notices or correspondence from any Governmental Authority requiring the termination, suspension or material modification of any studies, tests or preclinical or clinical trials conducted by or on behalf of the Company or its subsidiaries. All of the descriptions in the Pricing Disclosure Package and the Offering Memorandum of the legal and governmental procedures and requirements of the FDA or any foreign, state or local governmental body exercising comparable authority are accurate in all material respects.

(ee) Except as described in the Pricing Disclosure Package and the Offering Memorandum, there are no legal or governmental proceedings pending to which the Company or any of its subsidiaries is a party or of which any property or assets of the Company or any of its subsidiaries is the subject that would, in the aggregate, reasonably be expected to have a Material Adverse Effect or to have a material adverse effect on the performance by the Company of the performance of this Agreement, the Indenture, the Securities or the Registration Rights Agreement or the consummation of any of the transactions contemplated hereby; and to the Company's knowledge, no such proceedings are threatened in writing or contemplated by Governmental Authorities or others.

(ff) There are no legal or governmental proceedings or contracts or other documents that would be required to be described in a registration statement filed under the Securities Act or, in the case of documents, would be required to be filed as exhibits to a registration statement of the Company pursuant to Item 601(10) of Regulation S-K that have not been described or incorporated by reference in the Pricing Disclosure Package and the Offering Memorandum. Neither the Company nor any of its subsidiaries has knowledge that any other party to any such contract, agreement or arrangement has any intention not to render full performance as contemplated by the terms thereof; and that statements made or incorporated by

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reference in the Pricing Disclosure Package and the Offering Memorandum insofar as they purport to constitute summaries of the terms of statutes, rules or regulations, legal or governmental proceedings or contracts and other documents, constitute accurate summaries of the terms of such statutes, rules and regulations, legal and governmental proceedings and contracts and other documents in all material respects.

(gg) No relationship, direct or indirect, that would be required to be described in a registration statement of the Company pursuant to Item 404 of Regulation S-K, exists between or among the Company, on the one hand, and the directors, officers, stockholders, customers or suppliers of the Company, on the other hand, that has not been described in the Pricing Disclosure Package and the Offering Memorandum.

(hh) Except as described in the Pricing Disclosure Package and the Offering Memorandum, no labor disturbance by the employees of the Company or any of its subsidiaries exists or, to the knowledge of the Company, is imminent that would reasonably be expected to have a Material Adverse Effect.

(ii) (i) Each “employee benefit plan” (within the meaning of Section 3(3) of the Employee Retirement Security Act of 1974, as amended (“ERISA”)) for which the Company or any member of its “Controlled Group” (defined as any organization which is a member of a controlled group of corporations within the meaning of Section 414 of the Internal Revenue Code of 1986, as amended (the “Code”)) would have any liability (each a “Plan”) has been maintained in material compliance with its terms and with the requirements of all applicable statutes, rules and regulations including ERISA and the Code; (ii) with respect to each Plan subject to Title IV of ERISA (a) no “reportable event” (within the meaning of Section 4043(c) of ERISA) has occurred or is reasonably expected to occur, (b) no “accumulated funding deficiency” (within the meaning of Section 302 of ERISA or Section 412 of the Code), whether or not waived, has occurred or is reasonably expected to occur, (c) the fair market value of the assets under each Plan exceeds the present value of all benefits accrued under such Plan (determined based on those assumptions used to fund such Plan) and (d) neither the Company or any member of its Controlled Group has incurred, or reasonably expects to incur, any liability under Title IV of ERISA (other than contributions to the Plan or premiums to the Pension Benefit Guaranty Corporation in the ordinary course and without default) in respect of a Plan (including a “multiemployer plan,” within the meaning of Section 4001(c)(3) of ERISA); and (iii) each Plan that is intended to be qualified under Section 401(a) of the Code is so qualified and nothing has occurred, whether by action or by failure to act, which would cause the loss of such qualification.

(jj) The Company and each of its subsidiaries have filed all federal, state, local and foreign income and franchise tax returns required to be filed through the date hereof, subject to permitted extensions, and have paid all taxes due thereon, and no material tax deficiency has been determined adversely to the Company or any of its subsidiaries, nor does the Company have any knowledge of any tax deficiencies that would, in the aggregate, reasonably be expected to have a Material Adverse Effect.

(kk) There are no transfer taxes or other similar fees or charges under Federal law or the laws of any state, or any political subdivision thereof, required to be paid in

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connection with the execution and delivery of this Agreement or the issuance by the Company or sale by the Company of the Securities.

(ll) Since the date as of which information is given in the Pricing Disclosure Package and except as otherwise described in the Pricing Disclosure Package and the Offering Memorandum, the Company has not (i) issued or granted any securities, (ii) incurred any liability or obligation, direct or contingent, other than liabilities and obligations that were incurred in the ordinary course of business, (iii) entered into any material transaction not in the ordinary course of business or (iv) declared or paid any dividend on its capital stock.

(mm) The Company and each of its subsidiaries (i) make and keep accurate books and records and (ii) maintain and have maintained effective internal control over financial reporting as defined in Rule 13a-5 under the Exchange Act and a system of internal accounting controls sufficient to provide reasonable assurance that (A) transactions are executed in accordance with management’s general or specific authorization, (B) transactions are recorded as necessary to permit preparation of its financial statements in conformity with accounting principles generally accepted in the United States and to maintain accountability for its assets, (C) access to its assets is permitted only in accordance with management’s general or specific authorization, and (D) the reported accountability for its assets is compared with existing assets at reasonable intervals and appropriate action is taken with respect to any differences.

(nn) Neither the Company nor any of its subsidiaries (i) is in violation of its charter or by-laws (or similar organizational documents), (ii) is in default, and no event has occurred that, with notice or lapse of time or both, would constitute such a default, in the due performance or observance of any term, covenant, condition or other obligation contained in any indenture, mortgage, deed of trust, loan agreement, license or other agreement or instrument to which it is a party or by which it is bound or to which any of its properties or assets is subject or (iii) is in violation of any statute or any order, rule or regulation of any Governmental Authority or has failed to obtain any license, permit, certificate, franchise or other governmental authorization or permit necessary to the ownership of its property or to the conduct of its business, except in the case of clauses (ii) and (iii), to the extent any such conflict, breach, violation or default would not, in the aggregate, reasonably be expected to have a Material Adverse Effect.

(oo) Neither the Company nor any of its subsidiaries, nor, to the knowledge of the Company, any director, officer, agent, employee or other person acting on behalf of the Company or any of its subsidiaries, has (i) used any corporate funds for any unlawful contribution, gift, entertainment or other unlawful expense relating to political activity; (ii) made any direct or indirect unlawful payment to any foreign or domestic government official or employee from corporate funds; (iii) violated or is in violation of any provision of the Foreign Corrupt Practices Act of 1977; or (iv) made any bribe, rebate, payoff, influence payment, kickback or other unlawful payment.

(pp) The Company and each of its subsidiaries (i) are, and at all times prior hereto were, in compliance with all laws, regulations, ordinances, rules, orders, judgments, decrees, permits or other legal requirements of any Governmental Authority, including without limitation any international, national, state, provincial, regional, or local authority, relating to the

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protection of human health or safety, the environment, or natural resources, or to hazardous or toxic substances or wastes, pollutants or contaminants (“Environmental Laws”) applicable to such entity, which compliance includes, without limitation, obtaining, maintaining and complying with all permits and authorizations and approvals required by Environmental Laws to conduct their respective businesses, and (ii) have not received written notice of any actual or alleged violation of Environmental Laws, or of any potential liability for or other obligation concerning the presence, disposal or release of

hazardous or toxic substances or wastes, pollutants or contaminants, except in the case of clause (i) or (ii) where such non-compliance, violation, liability, or other obligation would not, in the aggregate, reasonably be expected to have a Material Adverse Effect. Except as described in the Pricing Disclosure Package and the Offering Memorandum, (A) there are no proceedings that are pending, or known to be contemplated, against the Company or any of its subsidiaries under Environmental Laws in which a Governmental Authority is also a party, other than such proceedings regarding which it is reasonably believed no monetary sanctions of \$250,000 or more will be imposed, (B) the Company and its subsidiaries are not aware of any issues regarding compliance with Environmental Laws, or liabilities or other obligations under Environmental Laws or concerning hazardous or toxic substances or wastes, pollutants or contaminants, that would reasonably be expected to have a Material Adverse Effect, and (C) none of the Company and its subsidiaries anticipates material capital expenditures relating to Environmental Laws.

(qq) None of the transactions contemplated by this Agreement (including, without limitation, the use of the proceeds from the sale of the Securities), will violate or result in a violation of Section 7 of the Exchange Act, or any regulation promulgated thereunder, including, without limitation, Regulations T, U and X of the Board of Governors of the Federal Reserve System.

(rr) The statements set forth in each of the Pricing Disclosure Package and the Offering Memorandum under the caption "Description of the Notes," insofar as they purport to constitute a summary of the terms of the Securities and under the captions "Description of Capital Stock," "Material U.S. Federal Tax Considerations," and "Plan of Distribution," insofar as they purport to describe the provisions of the laws and documents referred to therein, are accurate in all material respects.

(ss) The Company and its affiliates have not taken, directly or indirectly, any action (A) designed to or that has constituted or that reasonably can be expected to cause or result in the stabilization or manipulation of the price of any security of the Company in connection with the offering of the Securities to facilitate the sale or resale of such securities or (B) prohibited by Regulation M under the Exchange Act.

(tt) (i) The Company and each of its subsidiaries have established and maintain disclosure controls and procedures (as such term is defined in Rule 13a-15 under the Exchange Act), (ii) such disclosure controls and procedures are designed to ensure that the information required to be disclosed by the Company in the reports they file or submit under the Exchange Act (assuming the Company was required to file or submit such reports under the Exchange Act) is accumulated and communicated to management of the Company and its subsidiaries, including their respective principal executive officers and principal financial officers, as appropriate, to allow timely decisions regarding required disclosure to be made; and

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(iii) such disclosure controls and procedures are effective in all material respects to perform the functions for which they were established.

(uu) Since the date of the most recent balance sheet of the Company and its consolidated subsidiaries reviewed or audited by Ernst & Young LLP and the audit committee of the board of directors of the Company, (i) the Company has not been advised of (A) any significant deficiencies in the design or operation of internal controls that would adversely affect the ability of the Company or any of its subsidiaries to record, process, summarize and report financial data, or any material weaknesses in internal controls or (B) any fraud, whether or not material, that involves management or other employees who have a significant role in the internal controls of the Company and each of its subsidiaries, and (ii) since that date, there have been no significant changes in internal controls or in other factors that would significantly affect internal controls, including any corrective actions with regard to significant deficiencies and material weaknesses.

(vv) No subsidiary of the Company is currently prohibited, directly or indirectly, from paying any dividends to the Company, from making any other distribution on such subsidiary's capital stock, from repaying to the Company any loans or advances to such subsidiary from the Company or from transferring any of such subsidiary's property or assets to the Company or any other subsidiary of the Company, except as described in the Pricing Disclosure Package.

(ww) There is and has been no failure on the part of the Company and any of the Company's directors or officers, in their capacities as such, to comply in all material respects with the provisions of the Sarbanes-Oxley Act of 2002 and the rules and regulations promulgated in connection therewith.

(xx) Neither the Company nor any subsidiary is in violation of or has received notice of any violation with respect to any federal or state law relating to discrimination in the hiring, promotion or pay of employees, nor any applicable federal or state wage and hour laws, nor any state law precluding the denial of credit due to the neighborhood in which a property is situated, the violation of any of which would reasonably be expected to have a Material Adverse Effect.

(yy) The operations of the Company and its subsidiaries are and have been conducted at all times in compliance with applicable financial recordkeeping and reporting requirements of the Currency and Foreign Transactions Reporting Act of 1970, as amended, the money laundering statutes of all jurisdictions, the rules and regulations thereunder and any related or similar rules, regulations or guidelines, issued, administered or enforced by any Governmental Authority (collectively, the "**Money Laundering Laws**") and no action, suit or proceeding by or before any Governmental Authority involving the Company or any of its subsidiaries with respect to the Money Laundering Laws is pending or, to the knowledge of the Company, threatened, except, in each case, as would not reasonably be expected to have a Material Adverse Effect.

(zz) Neither the Company nor any of its subsidiaries nor, to the knowledge of the Company, any director, officer, agent, employee or affiliate of the Company or any of its

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subsidiaries is currently subject to any U.S. sanctions administered by the Office of Foreign Assets Control of the U.S. Treasury Department ("**OFAC**"); and the Company will not directly or indirectly use the proceeds of the offering, or lend, contribute or otherwise make available such proceeds to any subsidiary,

joint venture partner or other person or entity, for the purpose of financing the activities of any person currently subject to any U.S. sanctions administered by OFAC.

(aaa) The Company does not own any “margin securities” as that term is defined in Regulation U of the Board of Governors of the Federal Reserve System (the “Federal Reserve Board”), and none of the proceeds of the sale of the Stock will be used, directly or indirectly, for the purpose of purchasing or carrying any margin security, for the purpose of reducing or retiring any indebtedness which was originally incurred to purchase or carry any margin security or for any other purpose which might cause any of the Stock to be considered a “purpose credit” within the meanings of Regulations T, U or X of the Federal Reserve Board.

(bbb) Each forward-looking statement (within the meaning of Section 27A of the 1933 Act and Section 21E of the 1934 Act) contained or incorporated by reference in the Pricing Disclosure Package and the Offering Memorandum has been made with a reasonable basis, at the time it was made, or has been disclosed in good faith, at the time it was disclosed.

(ccc) On and immediately after the Closing Date, each of the Company and its subsidiaries (after giving effect to the issuance of the Securities and to the other transactions related thereto as described in each of the Pricing Disclosure Package and the Offering Memorandum) will be Solvent. As used in this paragraph, the term “**Solvent**” means, with respect to a particular date, that on such date (i) the present fair market value (or present fair saleable value) of the assets of each of the Company and its subsidiaries is not less than the total amount required to pay the probable liabilities on its total existing debts and liabilities (including contingent liabilities) as they become absolute and matured, (ii) each of the Company and its subsidiaries is able to realize upon its assets and pay its debts and other liabilities, contingent obligations and commitments as they mature and become due in the normal course of business, (iii) assuming the sale of the Securities as contemplated by this Agreement and each of the Pricing Disclosure Package and the Offering Memorandum, neither the Company nor its subsidiaries is incurring debts or liabilities beyond its ability to pay as such debts and liabilities mature; and (iv) neither the Company nor its subsidiaries is engaged in any business or transaction, and neither of them is about to engage in any business or transaction, for which its property would constitute unreasonably small capital after giving due consideration to the prevailing practice in the industry in which each of the Company and its subsidiaries is engaged. In computing the amount of such contingent liabilities at any time, it is intended that such liabilities will be computed at the amount that, in the light of all the facts and circumstances existing at such time, represents the amount that can reasonably be expected to become an actual or matured liability.

Any certificate signed by any officer of the Company and specifically identified in and required to be delivered to the Representative under this Agreement or the Registration Rights Agreement in connection with the offering of the Securities shall be deemed a representation and warranty by the Company, as to matters covered thereby, to each Initial Purchaser.

3. *Purchase of the Securities by the Initial Purchasers, Agreements to Sell, Purchase and Resell.* (a) The Company hereby agrees, on the basis of the representations, warranties and agreements of the Initial Purchasers contained herein and subject to all the terms and conditions set forth herein, to issue and sell to the Initial Purchasers and, upon the basis of the representations, warranties and agreements of the Company herein contained and subject to all the terms and conditions set forth herein, each Initial Purchaser agrees, severally and not jointly, to purchase from the Company, at a purchase price of 97.0% of the principal amount thereof (the “**Purchase Price**”), the total principal amount of Securities set forth opposite the name of such Initial Purchaser in Schedule I hereto. The Company shall not be obligated to deliver any of the securities to be delivered hereunder except upon payment for all of the securities to be purchased as provided herein.

(b) On the basis of the representations and warranties contained in this Agreement, and subject to its terms and conditions, the Company agrees to sell to the Initial Purchasers the Additional Securities, and the Initial Purchasers shall have the right to purchase, severally and not jointly, up to \$37,500,000 aggregate principal amount of Additional Securities at the Purchase Price. The Representative may exercise this right on behalf of the Initial Purchasers in whole or from time to time in part by giving written notice not later than 30 days after the date of this Agreement. Any exercise notice shall specify the principal amount of Additional Securities to be purchased by the Initial Purchasers and the date on which such Additional Securities are to be purchased. Each purchase date must be at least one business day after the written notice is given and may not be earlier than the closing date for the Firm Securities nor later than ten business days after the date of such notice. On each day, if any, that Additional Securities are to be purchased (an “**Option Closing Date**”), each Initial Purchaser agrees, severally and not jointly, to purchase the principal amount of Additional Securities (subject to such adjustments to eliminate fractional Securities as you may determine) that bears the same proportion to the total principal amount of Additional Securities to be purchased on such Option Closing Date as the principal amount of Firm Securities set forth in Schedule I opposite the name of such Initial Purchaser bears to the total principal amount of Firm Securities.

(c) Each of the Initial Purchasers, severally and not jointly hereby represents and warrants to the Company that it will offer the Securities for sale upon the terms and conditions set forth in this Agreement and in the Pricing Disclosure Package. Each of the Initial Purchasers hereby represents and warrants to, and agrees with, the Company, that such Initial Purchaser: (i) on the basis of the representations, warranties and agreements of the Company, is purchasing the Securities pursuant to a private sale exempt from registration under the Securities Act; (ii) is a QIB with such knowledge and experience in financial and business matters as are necessary in order to evaluate the merits and risks of an investment in the Securities; (iii) in connection with the Exempt Resales, will solicit offers to buy the Securities only from, and will offer to sell the Securities only to, the Eligible Purchasers in accordance with this Agreement and on the terms contemplated by the Pricing Disclosure Package; and (iv) will not directly or indirectly offer or sell the Securities, nor has it offered or sold the Securities by, or otherwise engaged in, any form of general solicitation or general advertising (within the meaning of Regulation D, including, but not limited to, advertisements, articles, notices or other communications published in any newspaper, magazine, or similar medium or broadcast over television or radio, or any seminar or meeting whose attendees have been invited by any general solicitation or general advertising). The Initial Purchasers have advised the Company that they

will offer the Securities to Eligible Purchasers at a price initially equal to 100% of the principal amount thereof, plus accrued interest, if any, from the date of issuance of the Securities. Such price may be changed by the Initial Purchasers at any time without notice.

(d) Each such Initial Purchaser has not nor, prior to the later to occur of (A) the Closing Date and (B) completion of the distribution of the Securities, will not, use, authorize use of, refer to or distribute any material in connection with the offering and sale of the Securities other than (i) the Preliminary Offering Memorandum, the Pricing Disclosure Package, the Offering Memorandum, (ii) any written communication that contains no "issuer information" (as defined in Rule 433(h)(2) under the Act) that was not included (including through incorporation by reference) in the Preliminary Offering Memorandum or any Free Writing Offering Document listed on Schedule III hereto, (iii) the Free Writing Offering Documents listed on Schedule III hereto, (iv) any written communication prepared by such Initial Purchaser and approved by the Company in writing, or (v) any written communication relating to or that contains the terms of the Securities and/or other information that was included (including through incorporation by reference) in the Preliminary Offering Memorandum, the Pricing Disclosure Package or the Offering Memorandum. Each such use of documents in this section shall be made only in accordance with Section 3(c)(iv).

Each of the Initial Purchasers understands that the Company and, for purposes of the opinions to be delivered to the Initial Purchasers pursuant to Sections 8(c) and 8(d) hereof, counsel to the Company and counsel to the Initial Purchasers, will rely upon the accuracy and truth of the foregoing representations, warranties and agreements, and the Initial Purchasers hereby consent to such reliance.

4. *Delivery of the Securities and Payment Therefor.* Delivery to the Initial Purchasers of and payment for the Firm Securities shall be made at the office of Latham & Watkins LLP, 12636 High Bluff Drive, Suite 400, San Diego, California 92130, at 10:00 a.m., New York City time, on January 23, 2007 (the "**Closing Date**"). The place of closing for the Securities and the Closing Date may be varied by agreement between the Initial Purchasers and the Company.

Payment for any Additional Securities shall be made to the Company against delivery of such Additional Securities for the respective accounts of the several Initial Purchasers at 10:00 a.m., New York City time, on the date specified in the corresponding notice described in Section 3(a) or at such other time on the same or on such other date, as may be varied by agreement between the Initial Purchasers and the Company.

The Securities will be delivered to the Initial Purchasers, or the Trustee as custodian for The Depository Trust Company ("**DTC**"), against payment by or on behalf of the Initial Purchasers of the purchase price therefor by wire transfer in immediately available funds, by causing DTC to credit the applicable Securities to the account of the Initial Purchasers at DTC. The Securities will be evidenced by one or more global securities in definitive form (the "**Global Securities**") or by additional definitive securities, and will be registered, in the case of the Global Securities, in the name of Cede & Co. as nominee of DTC, and in the other cases, in such names and in such denominations as the Initial Purchasers shall request prior to 9:30 a.m., New York City time, on the second business day preceding the Closing Date or the Option

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Closing Date, as the case may be. The Securities to be delivered to the Initial Purchasers shall be made available to the Initial Purchasers in New York City for inspection and packaging not later than 9:30 a.m., New York City time, on the business day next preceding the Closing Date or the Option Closing Date, as the case may be.

5. *Agreements of the Company.* The Company agrees with each of the Initial Purchasers as follows:

(a) The Company will furnish (which may be satisfied through electronic means) to the Initial Purchasers, without charge, within one business day of the date of the Offering Memorandum, such number of copies of the Offering Memorandum as may then be amended or supplemented as they may reasonably request.

(b) The Company will not make any amendment or supplement to the Pricing Disclosure Package or to the Offering Memorandum of which the Initial Purchasers shall not previously have been advised or to which they shall reasonably object after being so advised; *except* that the Company will be able to file any current report on Form 8-K, that the Company's counsel determines is required to be filed by the Company.

(c) The Company consents to the use of the Pricing Disclosure Package and the Offering Memorandum in accordance with the securities or Blue Sky laws of the jurisdictions in which the Securities are offered by the Initial Purchasers and by all dealers to whom Securities may be sold, in connection with the offering and sale of the Securities.

(d) If, at any time prior to completion of the distribution of the Securities by the Initial Purchasers to Eligible Purchasers, any event occurs or information becomes known that, in the judgment of the Company or in the opinion of counsel for the Initial Purchasers, should be set forth in the Pricing Disclosure Package or the Offering Memorandum so that the Pricing Disclosure Package or the Offering Memorandum, as then amended or supplemented, does not include any untrue statement of material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading, or if it is necessary to supplement or amend the Pricing Disclosure Package or the Offering Memorandum in order to comply with any law, the Company will forthwith prepare an appropriate supplement or amendment thereto, and will expeditiously furnish to the Initial Purchasers and dealers a reasonable number of copies thereof.

(e) The Company will not make any offer to sell or solicitation of an offer to buy the Securities that would constitute a Free Writing Offering Document without the prior consent of the Representative, which consent shall not be unreasonably withheld or delayed; if at any time following issuance of a Free Writing Offering Document any event occurred or occurs as a result of which such Free Writing Offering Document conflicts with the information in the Preliminary Offering Memorandum, the Pricing Disclosure Package or the Offering Memorandum or, when taken together with the information in the Preliminary Offering Memorandum, the Pricing Disclosure Package or the Offering Memorandum, includes an untrue statement of a material fact or omits to state any material fact necessary in order to make the statements therein, in the light of the circumstances then prevailing, not misleading, as promptly as practicable after becoming aware thereof, the Company will give notice thereof to the Initial

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Purchasers through the Representative and, if requested by the Representative, will prepare and furnish without charge to each Initial Purchaser a Free Writing Offering Document or other document which will correct such conflict, statement or omission.

(f) Promptly from time to time to take such action as the Initial Purchasers may reasonably request to qualify the Securities for offering and sale under the securities or Blue Sky laws of such jurisdictions as the Initial Purchasers may request and to comply with such laws so as to permit the continuance of sales and dealings therein in such jurisdictions for as long as may be necessary to complete the distribution of the Securities; *provided* that in connection therewith the Company shall not be required to (i) qualify as a foreign corporation in any jurisdiction in which it would not otherwise be required to so qualify, (ii) file a general consent to service of process in any such jurisdiction or (iii) subject itself to taxation in any jurisdiction in which it would not otherwise be subject.

(g) For a period commencing on the date hereof and ending on the 90th day after the date of the Offering Memorandum (the “**Lock-up Period**”), the Company agrees not to, directly or indirectly, (1) offer for sale, sell, or otherwise dispose of (or enter into any transaction or device that is designed to, or would be expected to, result in the disposition by any person at any time in the future of) any common stock (par value \$0.001 per share) of the Company or securities convertible into or exchangeable for such common stock of the Company, or sell or grant options, rights or warrants with respect to the common stock of the Company or securities convertible into or exchangeable for the common stock of the Company, (2) enter into any swap or other derivatives transaction that transfers to another, in whole or in part, any of the economic benefits or risks of ownership of the common stock of the Company, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of common stock securities of the Company or other securities, in cash or otherwise, (3) file or cause to be filed a registration statement (other than on Form S-8 or any successor form or the registration statement contemplated by the Registration Rights Agreement), with respect to the registration of common stock of the Company or securities convertible, exercisable or exchangeable into shares of common stock of the Company or (4) publicly announce an offering of any shares of common stock of the Company or securities convertible or exchangeable into shares of common stock of the Company, in each case without the prior written consent of Lehman Brothers Inc., on behalf of the Initial Purchasers, except that a subsidiary of the Company may sell equity securities exchangeable for the Company’s common stock, so long as such exchange cannot occur until after the expiry of the Lock-up Period. The Company will cause each officer and director of the Company set forth on Schedule IV hereto to furnish to Lehman Brothers Inc., prior to the Closing Date, a letter or letters, substantially in the form of Exhibit B hereto (the “**Lock-Up Agreements**”).

(h) The Company will furnish to the holders of the Securities as soon as practicable after the end of each fiscal year an annual report (including a balance sheet and statements of income, stockholders’ equity and cash flows of the Company and its consolidated subsidiaries certified by independent public accountants) and, as soon as practicable after the end of each of the first three quarters of each fiscal year (beginning with the fiscal quarter ending after the date of the Offering Memorandum), will make available to its securityholders consolidated summary financial information of the Company and its subsidiaries for such quarter in reasonable detail; *provided* that so long as the Company files periodic reports pursuant to

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Section 13 or 15(d) of the Exchange Act for the foregoing periods, the Company shall be deemed to comply with this Section 5(h).

(i) So long as any of the Securities or the Underlying Securities are outstanding, the Company will furnish to the Initial Purchasers (i) as soon as available, a copy of each report of the Company mailed to stockholders generally or filed with any stock exchange or regulatory body and (ii) from time to time such other information concerning the Company as the Initial Purchasers may reasonably request. The Company may satisfy its obligations to furnish such reports by filing them on the Commission’s electronic data gathering and retrieval system (EDGAR).

(j) The Company will apply the net proceeds from the sale of the Securities to be sold by it hereunder substantially in accordance with the description set forth in the Pricing Disclosure Package and the Offering Memorandum under the caption “Use of Proceeds.”

(k) The Company and its affiliates will not take, directly or indirectly, any action designed to or that has constituted or that reasonably would be expected to cause or result in the stabilization or manipulation of the price of any security of the Company in connection with the offering of the Securities.

(l) The Company will use its best efforts to permit the Securities to be designated as Private Offerings, Resales and Trading through Automated Linkages (PORTAL) MarketSM (the “**PORTAL Market**SM”) securities in accordance with the rules and regulations adopted by the National Association of Securities Dealers, Inc. relating to trading in the PORTAL MarketSM and to permit the Securities to be eligible for clearance and settlement through DTC.

(m) The Company will not, and will not permit any of its affiliates (as defined in Rule 144 under the Securities Act) to, resell any of the Securities that have been acquired by any of them, except for Securities purchased by the Company or any of its affiliates and resold in a transaction registered under the Securities Act.

(n) The Company agree not to sell, offer for sale or solicit offers to buy or otherwise negotiate in respect of any security (as defined in the Securities Act) that would be integrated with the sale of the Securities in a manner that would require the registration under the Securities Act of the sale to the Initial Purchasers or the Eligible Purchasers of the Securities.

(o) The Company agrees to comply with all the terms and conditions of the Registration Rights Agreement and all agreements set forth in the representation letters of the Company to DTC relating to the approval of the Securities by DTC for “book entry” transfer.

(p) The Company will take such steps as shall be necessary to ensure that neither the Company nor any of its subsidiaries becomes an “investment company” within the meaning of such term under the Investment Company Act of 1940, as amended.

(q) The Company will do and perform all things required or necessary to be done and performed under this Agreement by it prior to the Closing Date, and to satisfy all conditions precedent to the Initial Purchasers’ obligations hereunder to purchase the Securities.

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6. *Expenses.* Whether or not the transactions contemplated by this Agreement are consummated or this Agreement becomes effective or is terminated, the Company agrees, to pay all costs, expenses, fees and taxes incident to and in connection with: (i) the preparation, printing, filing and distribution of the Preliminary Offering Memorandum, the Pricing Disclosure Package and the Offering Memorandum (including, without limitation, financial statements and exhibits) and all amendments and supplements thereto (including the fees, disbursements and expenses of the Company's accountants and counsel, but not, however, legal fees and expenses of the Initial Purchasers' counsel incurred in connection therewith); (ii) the preparation, printing (including, without limitation, word processing and duplication costs) and delivery of this Agreement, the Indenture, the Registration Rights Agreement, all Blue Sky memoranda and all other agreements, memoranda, correspondence and other documents printed and delivered in connection therewith and with the Exempt Resales (but not, however, legal fees and expenses of the Initial Purchasers' counsel incurred in connection with any of the foregoing other than fees of such counsel plus reasonable disbursements incurred in connection with the preparation, printing and delivery of such Blue Sky memoranda, not to exceed \$7,500); (iii) the issuance and delivery by the Company of the Securities and any taxes payable in connection therewith; (iv) the qualification of the Securities for offer and sale under the securities or Blue Sky laws of the several states (including, without limitation, the reasonable fees and disbursements of the Initial Purchasers' counsel relating to such registration or qualification); (v) the furnishing of such copies of the Pricing Disclosure Package and the Offering Memorandum, and all amendments and supplements thereto, as may be reasonably requested for use in connection with the Exempt Resales; (vi) the preparation of certificates for the Securities (including, without limitation, printing and engraving thereof); (vii) the application for quotation of the Securities in the PORTAL MarketSM (including all disbursements and listing fees); (viii) the approval of the Securities by DTC for "book-entry" transfer (including fees and expenses of counsel); (ix) the rating of the Securities; (x) the obligations of the Trustee, any agent of the Trustee and the counsel for the Trustee in connection with the Indenture and the Securities; (xi) the performance by the Company of their other obligations under this Agreement; and (xii) all travel expenses (consistent with the Company's travel policy) of each Initial Purchaser and the Company's officers and employees and any other expenses of each Initial Purchaser and the Company in connection with attending or hosting meetings with prospective purchasers of the Securities, and expenses associated with any electronic road show.

7. *Conditions to Initial Purchasers' Obligations.* The respective obligations of the Initial Purchasers hereunder are subject to the accuracy, when made and on and as of the Closing Date, of the representations and warranties of the Company contained herein, to the performance by the Company of its obligations hereunder, and to each of the following additional terms and conditions:

(a) The Initial Purchasers shall not have discovered and disclosed to the Company on or prior to the Closing Date that the Pricing Disclosure Package or the Offering Memorandum, or any amendment or supplement thereto, contains an untrue statement of a fact which, in the opinion of Latham & Watkins LLP, counsel to the Initial Purchasers, is material or omits to state a fact which, in the opinion of such counsel, is material and is necessary to make the statements therein not misleading.

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(b) All corporate proceedings and other legal matters incident to the authorization, form and validity of this Agreement, the Securities, the Registration Rights Agreement, the Indenture, the Pricing Disclosure Package and the Offering Memorandum, and all other legal matters relating to this Agreement and the transactions contemplated hereby shall be reasonably satisfactory in all material respects to counsel for the Initial Purchasers, and the Company shall have furnished to such counsel all documents and information that they may reasonably request to enable them to pass upon such matters.

(c) (i) Cooley Godward Kronish LLP shall have furnished to the Initial Purchasers its written opinion, as counsel to the Company, addressed to the Initial Purchasers and dated the Closing Date, substantially in the form of Exhibit C-1 hereto.

(ii) Grantland Bryce, General Counsel of the Company, shall have furnished to the Initial Purchasers its written opinion, as counsel to the Company, addressed to the Initial Purchasers and dated the Closing Date, substantially in the form of Exhibit C-2 hereto.

(d) (i) Knobbe Martens Olson & Bear shall have furnished to the Initial Purchasers its written opinion, as intellectual property counsel to the Company, addressed to the Initial Purchasers and dated the Closing Date, substantially in the form of Exhibit D-1 hereto.

(ii) The Elmore Patent Law Group shall have furnished to the Initial Purchasers its written opinion, as intellectual property counsel to the Company, addressed to the Initial Purchasers and dated the Closing Date, substantially in the form of Exhibit D-2 hereto.

(e) The Initial Purchasers shall have received from Latham & Watkins LLP, counsel for the Initial Purchasers, such opinion or opinions, dated the Closing Date, with respect to the issuance and sale of the Securities, the Pricing Disclosure Package, the Offering Memorandum and other related matters as the Initial Purchasers may reasonably require, and the Company shall have furnished to such counsel such documents and information as they reasonably request for the purpose of enabling them to pass upon such matters.

(f) At the time of execution of this Agreement, the Initial Purchasers shall have received from Ernst & Young LLP a letter, in form and substance satisfactory to the Initial Purchasers, addressed to the Initial Purchasers and dated the date hereof (i) confirming that they are independent public accountants within the meaning of the Securities Act and are in compliance with the applicable requirements relating to the qualification of accountants under Rule 2-01 of Regulation S-X of the Commission and (ii) stating, as of the date hereof (or, with respect to matters involving changes or developments since the respective dates as of which specified financial information is given in the Pricing Disclosure Package, as of a date not more than three days prior to the date hereof), the conclusions and findings of such firm with respect to the financial information and (iii) covering such other matters as are ordinarily covered by accountants' "comfort letters" to underwriters in connection with registered public offerings.

(g) With respect to the letter of Ernst & Young LLP referred to in the preceding paragraph and delivered to the Initial Purchasers concurrently with the execution of this Agreement (the "**initial letter**"), the Company shall have furnished to the Initial Purchasers a letter (the "**bring-down letter**") of such accountants, addressed to the Initial Purchasers and

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dated the Closing Date (i) confirming that they are independent public accountants within the meaning of the Securities Act and are in compliance with the applicable requirements relating to the qualification of accountants under Rule 2-01 of Regulation S-X of the Commission, (ii) stating, as of the Closing Date (or, with respect to matters involving changes or developments since the respective dates as of which specified financial information is given in each of the Pricing Disclosure Package or the Offering Memorandum, as of a date not more than three days prior to the date of the Closing Date), the conclusions and findings of such firm with respect to the financial information and other matters covered by the initial letter and (iii) confirming in all material respects the conclusions and findings set forth in the initial letter.

(h) Except as described in the Pricing Disclosure Package, (i) neither the Company nor any of its subsidiaries shall have sustained, since the date of the latest audited financial statements included in the Pricing Disclosure Package, any loss or interference with its business from fire, explosion, flood or other calamity, whether or not covered by insurance, or from any labor dispute or court or governmental action, order or decree or (ii) since such date, there shall not have been any change in the capital stock or long-term debt of the Company or any of its subsidiaries or any change, or any development involving a prospective change, in or affecting the condition (financial or otherwise), results of operations, stockholders' equity, properties, management, business or prospects of the Company and its subsidiaries, taken as a whole, the effect of which, in any such case described in clause (i) or (ii), is, individually or in the aggregate, in the judgment of the Representative, so material and adverse as to make it impracticable or inadvisable to proceed with the offering or the delivery of the Securities being delivered on the Closing Date on the terms and in the manner contemplated in the Offering Memorandum.

(i) The Company shall have furnished or caused to be furnished to the Initial Purchasers on the Closing Date certificates of an executive officer of the Company stating that:

(i) The representations, warranties and agreements of the Company in Section 2 are true and correct on and as of the Closing Date, and the Company has complied with all the agreements contained herein and satisfied all the conditions on its part required hereunder to be performed or satisfied hereunder at or prior to the Closing Date; and

(ii) They have examined the Pricing Disclosure Package and the Offering Memorandum, and, in their opinion, (A) the Pricing Disclosure Package, as of the Applicable Time and as of the Closing Date, and the Offering Memorandum, as of its date and as of the Closing Date, did not and do not contain any untrue statement of a material fact and did not and do not omit to state a material fact necessary to make the statements therein, in the light of the circumstances under which they were made, not misleading and (B) since the Applicable Time with respect to the Pricing Disclosure Package and the date of the Offering Memorandum with respect to the Offering Memorandum, no event has occurred which should have been set forth in a supplement or amendment to the Pricing Disclosure Package or the Offering Memorandum that has not been so disclosed; *provided* that no representation or warranty is made as to information contained in or omitted from either the Pricing Disclosure Package or the Offering Memorandum in reliance upon and in conformity with written information furnished to the Company through the Representative by or on behalf of any Initial Purchaser specifically for inclusion therein, which information is specified in Section 8(e); and

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(iii) Except as described in each of the Pricing Disclosure Package and the Offering Memorandum, (A) neither the Company nor any of its subsidiaries shall have sustained, since the date of the latest audited financial statements included in the Pricing Disclosure Package, any loss or interference with its business from fire, explosion, flood or other calamity, whether or not covered by insurance, or from any labor dispute or court or governmental action, order or decree or (B) since such date, there shall not have been any change in the capital stock or long-term debt of the Company or any of its subsidiaries or any change, or any development involving a prospective change, in or affecting the condition (financial or otherwise), results of operations, stockholders' equity, properties, management, business or prospects of the Company and its subsidiaries, taken as a whole, the effect of which, in any such case described in clause (A) or (B), is, individually or in the aggregate, in their judgment, so material and adverse as to make it impracticable or inadvisable to proceed with the offering or the delivery of the Securities being delivered on the Closing Date on the terms and in the manner contemplated in the Offering Memorandum.

(j) The Securities shall have been designated for trading on the PORTAL MarketSM.

(k) The Company shall have executed and delivered the Registration Rights Agreement, and the Initial Purchasers shall have received a copy thereof, duly executed by the Company (with an original signature page to follow).

(l) The Company and the Trustee shall have executed and delivered the Indenture, and the Initial Purchasers shall have received a copy thereof, duly executed by the Company and the Trustee (with an original signature page to follow).

(m) Subsequent to the execution and delivery of this Agreement there shall not have occurred any of the following: (i) trading in securities generally on the New York Stock Exchange or the American Stock Exchange or in the over-the-counter market, or trading in any securities of the Company on any exchange or in the over-the-counter market, shall have been suspended or materially limited or the settlement of such trading generally shall have been materially disrupted or minimum prices shall have been established on any such exchange or such market by the Commission, by such exchange or by any other regulatory body or Governmental Authority having jurisdiction, (ii) a banking moratorium shall have been declared by federal or state authorities, (iii) the United States shall have become engaged in hostilities, there shall have been an escalation in hostilities involving the United States or there shall have been a declaration of a national emergency or war by the United States or (iv) there shall have occurred such a material adverse change in general economic, political or financial conditions, including, without limitation, as a result of terrorist activities after the date hereof (or the effect of international conditions on the financial markets in the United States shall be such), as to make it, in the judgment of the Representative, impracticable or inadvisable to proceed with the offering or delivery of the Securities being delivered on the Closing Date on the terms and in the manner contemplated in the Offering Memorandum or that, in the judgment of the Representative, would materially and adversely affect the financial markets or the markets for the Securities and other debt securities.

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(n) The Company shall have furnished to the Initial Purchasers a certificate dated the Closing Date, of the Chief Financial Officer of the Company as to the solvency of the Company following the consummation of the transactions.

The several obligations of the Initial Purchasers to purchase Additional Securities hereunder are subject to the delivery to the Representative on the applicable Option Closing Date of such documents as the Representative may reasonably request with respect to the good standing of the Company, the due authorization and issuance of the Additional Securities to be sold on such Option Closing Date and other matters related to the issuance of such Additional Securities.

8. *Indemnification and Contribution.*

(a) The Company hereby agrees to indemnify and hold harmless each Initial Purchaser, its directors, officers and employees and each person, if any, who controls any Initial Purchaser within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act, from and against any loss, claim, damage or liability, joint or several, or any action in respect thereof (including, but not limited to, any loss, claim, damage, liability or action relating to purchases and sales of the Securities), to which that Initial Purchaser, director, officer, employee or controlling person may become subject, under the Securities Act, the Exchange Act or otherwise, insofar as such loss, claim, damage, liability or action arises out of, or is based upon, (i) any untrue statement or alleged untrue statement of a material fact contained in (A) the Pricing Disclosure Package or the Offering Memorandum or in any amendment or supplement thereto, (B) any Blue Sky application or other document prepared or executed by the Company (or based upon any written information furnished by the Company) specifically for the purpose of qualifying any or all of the Securities under the securities laws of any state or other jurisdiction (any such application, document or information being hereinafter called a “**Blue Sky Application**”) or (C) any roadshow or investor presentations made to investors by the Company (whether in person or electronically) (“**Marketing Materials**”), or (ii) the omission or alleged omission to state in the Pricing Disclosure Package or the Offering Memorandum, or in any amendment or supplement thereto, or in any Blue Sky Application or in any Marketing Materials, any material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading, and shall reimburse each Initial Purchaser and each such director, officer, employee or controlling person promptly upon demand for any legal or other expenses reasonably incurred by that Initial Purchaser, director, officer, employee or controlling person in connection with investigating or defending or preparing to defend against any such loss, claim, damage, liability or action as such expenses are incurred; *provided*, that the Company shall not be liable in any such case to the extent that any such loss, claim, damage, liability or action arises out of, or is based upon, any untrue statement or alleged untrue statement or omission or alleged omission made in the Pricing Disclosure Package or the Offering Memorandum, or in any such amendment or supplement thereto, or in any Blue Sky Application or in any Marketing Materials, in reliance upon and in conformity with written information concerning such Initial Purchaser furnished to the Company through the Representative by or on behalf of any Initial Purchaser specifically for inclusion therein, which information consists solely of the information specified in Section 8(e). The foregoing indemnity agreement is in addition to any liability that the Company may otherwise have to any

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Initial Purchaser or to any director, officer, employee or controlling person of that Initial Purchaser.

(b) Each Initial Purchaser, severally and not jointly, hereby agrees to indemnify and hold harmless the Company, its officers and employees, each of its directors, and each person, if any, who controls the Company within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act, from and against any loss, claim, damage or liability, joint or several, or any action in respect thereof, to which the Company or any such director, officer, employee or controlling person may become subject, under the Securities Act, the Exchange Act or otherwise, insofar as such loss, claim, damage, liability or action arises out of, or is based upon, (i) any untrue statement or alleged untrue statement of a material fact contained in (A) the Pricing Disclosure Package or the Offering Memorandum or in any amendment or supplement thereto, (B) any Blue Sky Application, or (C) any Marketing Materials or (ii) the omission or alleged omission to state in the Pricing Disclosure Package or the Offering Memorandum, or in any amendment or supplement thereto, or in any Blue Sky Application or in any Marketing Materials any material fact necessary to make the statements therein not misleading, but in each case only to the extent that the untrue statement or alleged untrue statement or omission or alleged omission was made in reliance upon and in conformity with written information concerning such Initial Purchaser furnished to the Company through the Representative by or on behalf of that Initial Purchaser specifically for inclusion therein, which information is limited to the information set forth in Section 8(e). The foregoing indemnity agreement is in addition to any liability that any Initial Purchaser may otherwise have to the Company or any such director, officer, employee or controlling person.

(c) Promptly after receipt by an indemnified party under this Section 8 of notice of any claim or the commencement of any action, the indemnified party shall, if a claim in respect thereof is to be made against the indemnifying party under this Section 8, notify the indemnifying party in writing of the claim or the commencement of that action; *provided*, that the failure to notify the indemnifying party shall not relieve it from any liability that it may have under this Section 8 except to the extent it has been materially prejudiced by such failure and; *provided, further*, that the failure to notify the indemnifying party shall not relieve it from any liability that it may have to an indemnified party otherwise than under this Section 8. If any such claim or action shall be brought against an indemnified party, and it shall notify the indemnifying party thereof, the indemnifying party shall be entitled to participate therein and, to the extent that it wishes, jointly with any other similarly notified indemnifying party, to assume the defense thereof with counsel reasonably satisfactory to the indemnified party. After notice from the indemnifying party to the indemnified party of its election to assume the defense of such claim or action, the indemnifying party shall not be liable to the indemnified party under this Section 8 for any legal or other expenses subsequently incurred by the indemnified party in connection with the defense thereof other than reasonable costs of investigation; *provided*, that the Initial Purchasers shall have the right to employ counsel to represent jointly the Initial Purchasers and their respective directors, officers, employees and controlling persons who may be subject to liability arising out of any claim in respect of which indemnity may be sought by the Initial Purchasers against the Company under this Section 8, if (i) the Company and the Initial Purchasers shall have so mutually agreed; (ii) the Company has failed within a reasonable time to retain counsel reasonably satisfactory to the Initial Purchasers; (iii) the Initial Purchasers and their respective directors, officers, employees and controlling persons shall have reasonably

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concluded, based on the advice of counsel, that there may be legal defenses available to them that are different from or in addition to those available to the Company; or (iv) the named parties in any such proceeding (including any impleaded parties) include both the Initial Purchasers or their respective directors,

officers, employees or controlling persons, on the one hand, and the Company, on the other hand, and representation of both sets of parties by the same counsel would present a conflict due to actual or potential differing interests between them, and in any such event the fees and expenses of such separate counsel shall be paid by the Company. No indemnifying party shall (i) without the prior written consent of the indemnified parties (which consent shall not be unreasonably withheld), settle or compromise or consent to the entry of any judgment with respect to any pending or threatened claim, action, suit or proceeding in respect of which indemnification or contribution may be sought hereunder (whether or not the indemnified parties are actual or potential parties to such claim or action) unless such settlement, compromise or consent includes an unconditional release of each indemnified party from all liability arising out of such claim, action, suit or proceeding, or (ii) be liable for any settlement of any such action effected without its written consent (which consent shall not be unreasonably withheld), but if settled with the consent of the indemnifying party or if there be a final judgment of the plaintiff in any such action, the indemnifying party agrees to indemnify and hold harmless any indemnified party from and against any loss or liability by reason of such settlement or judgment.

(d) If the indemnification provided for in this Section 8 shall for any reason be unavailable to or insufficient to hold harmless an indemnified party under Section 8(a) or 8(b) in respect of any loss, claim, damage or liability, or any action in respect thereof, referred to therein, then each 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 loss, claim, damage or liability, or action in respect thereof, (i) in such proportion as shall be appropriate to reflect the relative benefits received by the Company, on the one hand, and the Initial Purchasers, on the other, from the offering of the Securities or (ii) if the allocation provided by clause (i) above is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause (i) above but also the relative fault of the Company, on the one hand, and the Initial Purchasers, on the other, with respect to the statements or omissions that resulted in such loss, claim, damage or liability, or action in respect thereof, as well as any other relevant equitable considerations. The relative benefits received by the Company, on the one hand, and the Initial Purchasers, on the other, with respect to such offering shall be deemed to be in the same proportion as the total net proceeds from the offering of the Securities purchased under this Agreement (before deducting expenses) received by the Company, on the one hand, and the total underwriting discounts and commissions received by the Initial Purchasers with respect to the Securities purchased under this Agreement, on the other hand, bear to the total gross proceeds from the offering of the Securities under this Agreement as set forth on the cover page of the Offering Memorandum. The relative fault shall be determined by reference to whether the untrue or alleged untrue statement of a material fact or omission or alleged omission to state a material fact relates to information supplied by the Company, or the Initial Purchasers, the intent of the parties and their relative knowledge, access to information and opportunity to correct or prevent such statement or omission. The Company and the Initial Purchasers agree that it would not be just and equitable if contributions pursuant to this Section 8(d) were to be determined by pro rata allocation (even if the Initial Purchasers were treated as one entity for such purpose) or by any other method of

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allocation that does not take into account the equitable considerations referred to herein. The amount paid or payable by an indemnified party as a result of the loss, claim, damage or liability, or action in respect thereof, referred to above in this Section 8(d) shall be deemed to include, for purposes of this Section 8(d), any legal or other expenses reasonably incurred by such indemnified party in connection with investigating or defending any such action or claim. Notwithstanding the provisions of this Section 8(d), no Initial Purchaser shall be required to contribute any amount in excess of the amount by which the net proceeds from the sale to Eligible Purchasers of the Securities initially purchased by it exceeds the amount of any damages that such Initial Purchaser has otherwise paid or become liable to pay by reason of any untrue or alleged untrue statement or omission or alleged omission. 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. The Initial Purchasers' obligations to contribute as provided in this Section 8(d) are several in proportion to their respective underwriting obligations and not joint.

(e) The Initial Purchasers severally confirm and the Company acknowledges and agrees that the statements with respect to the offering of the Securities by the Initial Purchasers set forth in the second sentence of the third paragraph, the third sentence of the paragraph under the caption entitled "Restrictions on Resale" and the first paragraph under the caption entitled "Stabilization, Short Positions, Market Making and Trading" of the section entitled "Plan of Distribution" in the Pricing Disclosure Package and the Offering Memorandum are correct and constitute the only information concerning such Initial Purchasers furnished in writing to the Company by or on behalf of the Initial Purchasers specifically for inclusion in the Pricing Disclosure Package and the Offering Memorandum or in any amendment or supplement thereto.

9. *Defaulting Initial Purchasers.* If on the Closing Date, or on an Option Closing Date, as the case may be, any Initial Purchaser defaults in the performance of its obligations under this Agreement, the remaining non-defaulting Initial Purchasers shall be obligated to purchase the Securities that the defaulting Initial Purchaser agreed but failed to purchase on the Closing Date or the Option Closing Date, as the case may be, in the respective proportions that the principal amount of Securities set opposite the name of each remaining non-defaulting Initial Purchaser in Schedule I hereto bears to the total principal amount of Securities set opposite the names of all the remaining non-defaulting Initial Purchasers in Schedule I hereto; *provided*, that the remaining non-defaulting Initial Purchasers shall not be obligated to purchase any of the Securities on the Closing Date or the Option Closing Date, as the case may be, if the aggregate principal amount of Securities that the defaulting Initial Purchaser or Initial Purchasers agreed but failed to purchase on such date exceeds 9.09% of the aggregate principal amount of Securities to be purchased on the Closing Date, or on the Option Closing Date, as the case may be, and any remaining non-defaulting Initial Purchasers shall not be obligated to purchase more than 110% of the aggregate principal amount of Securities that it agreed to purchase on the Closing Date, or on the Option Closing Date, as the case may be, pursuant to the terms of Section 3. If the foregoing maximums are exceeded, the remaining non-defaulting Initial Purchasers, or those other Initial Purchasers satisfactory to the Initial Purchasers who so agree, shall have the right, but shall not be obligated, to purchase, in such proportion as may be agreed upon among them, all the Securities to be purchased on the Closing Date, or on the Option Closing Date, as the case may be.

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If other Initial Purchasers are obligated or agree to purchase the Securities of a defaulting or withdrawing Initial Purchaser, either the remaining Initial Purchasers or the Company may postpone the Closing Date for up to seven full business days in order to effect any changes that in the opinion of counsel for the Company or counsel for the Initial Purchasers may be necessary in the Pricing Disclosure Package, the Offering Memorandum or in any other document or arrangement.

If the remaining Initial Purchasers or other Initial Purchasers satisfactory to the Initial Purchasers do not elect to purchase: (a) the Securities that the defaulting Initial Purchaser or Initial Purchasers agreed but failed to purchase on the Closing Date, this Agreement shall terminate without liability on the part of any non-defaulting Initial Purchaser or the Company; or (b) the Additional Securities that the defaulting Initial Purchaser or Initial Purchasers agreed but failed to purchase on the Option Closing Date, the non-defaulting Initial Purchasers shall have, the option to either: (i) terminate their obligation hereunder to purchase the Additional Securities to be sold on such Option Closing Date; or (ii) purchase not less than the principal amount of Additional Securities that such non-defaulting Initial Purchaser would have been obligated to purchase in the absence of such default.

As used in this Agreement, the term "Initial Purchaser" includes, for all purposes of this Agreement unless the context requires otherwise, any party not listed in Schedule I hereto that, pursuant to this Section 10, purchases Securities that a defaulting Initial Purchaser agreed but failed to purchase.

Nothing contained herein shall relieve: (a) a defaulting Initial Purchaser of any liability it may have to the Company for damages caused by its default; or (b) the Company of any liability for the payment of expenses to the extent set forth in Sections 7 and 12.

10. *Termination.* The obligations of the Initial Purchasers hereunder may be terminated by the Initial Purchasers by notice given to and received by the Company prior to delivery of and payment for the Securities if, prior to that time, any of the events described in Sections 7(g) or (l) shall have occurred or if the Initial Purchasers shall decline to purchase the Securities for any reason permitted under this Agreement.

11. *Reimbursement of Initial Purchasers' Expenses.* If (a) the Company fails to tender the Securities for delivery to the Initial Purchasers or (b) the Initial Purchasers shall decline to purchase the Securities because any of the conditions set forth in Section 7 of this Agreement is not met, the Company shall reimburse the Initial Purchasers for all reasonable out-of-pocket expenses (including fees and disbursements of counsel) incurred by the Initial Purchasers in connection with this Agreement and the proposed purchase of the Securities, and upon demand the Company shall pay the full amount thereof to the Initial Purchasers.

12. *Notices, etc.* All statements, requests, notices and agreements hereunder shall be in writing, and:

(a) if to any Initial Purchaser, shall be delivered or sent by hand delivery, mail, telex, overnight courier or facsimile transmission to Lehman Brothers Inc., 745 Seventh Avenue, New York, New York 10019, Attention: Syndicate Registration (Fax: 646-834-8133)

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with a copy to Latham & Watkins LLP, 12636 High Bluff Drive, Suite 400, San Diego, California 92130, Attention: Faye H. Russell (Fax: 858-523-5450), and with a copy, in the case of any notice pursuant to Section 8(c), to the Director of Litigation, Office of the General Counsel, Lehman Brothers Inc., 399 Park Avenue, 10th Floor, New York, New York 10022 (Fax: 212-520-0421);

(b) if to the Company, shall be delivered or sent by mail, telex, overnight courier or facsimile transmission to Isis Pharmaceuticals, Inc., 1896 Rutherford Road, Carlsbad, California 92008, Attention: B. Lynne Parshall (Fax: 760-603-4650), with a copy to (i) General Counsel (Fax: 760-268-4922) and (ii) Cooley Godward Kronish LLP, 4401 Eastgate Mall, San Diego, California 92121, Attention: Julie M. Robinson (Fax: 858-550-6420);

provided, that any notice to an Initial Purchaser pursuant to Section 8(c) shall be delivered or sent by hand delivery, mail, telex or facsimile transmission to such Initial Purchaser at its address set forth in its acceptance telex to Lehman Brothers Inc., which address will be supplied to any other party hereto by Lehman Brothers Inc. upon request. Any such statements, requests, notices or agreements shall take effect at the time of receipt thereof. The Company shall be entitled to act and rely upon any request, consent, notice or agreement given or made on behalf of the Initial Purchasers by Lehman Brothers Inc.

13. *Persons Entitled to Benefit of Agreement.* This Agreement shall inure to the benefit of and be binding upon the Initial Purchasers, the Company, and their respective successors. This Agreement and the terms and provisions hereof are for the sole benefit of only those persons, except that the representations, warranties, indemnities and agreements of the Company contained in this Agreement shall also be deemed to be for the benefit of directors, officers and employees of the Initial Purchasers and each person or persons, if any, controlling any Initial Purchaser within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act to the extent necessary for such person to exercise its rights under Section 8 hereof. Nothing in this Agreement is intended or shall be construed to give any person, other than the persons referred to in this Section 14, any legal or equitable right, remedy or claim under or in respect of this Agreement or any provision contained herein.

14. *Survival.* The respective indemnities, representations, warranties and agreements of the Company and the Initial Purchasers contained in this Agreement or made by or on behalf on them, respectively, pursuant to this Agreement, shall survive the delivery of and payment for the Securities and shall remain in full force and effect, regardless of any investigation made by or on behalf of any of them or any person controlling any of them.

15. *Definition of the Terms "Business Day," "Affiliate" and "Subsidiary."* For purposes of this Agreement, (a) "business day" means any day on which the New York Stock Exchange, Inc. is open for trading and (b) "affiliate" and "subsidiary" have the meanings set forth in Rule 405 under the Securities Act.

16. *Governing Law.* **This Agreement shall be governed by and construed in accordance with the laws of New York.**

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17. *No Fiduciary Duty.* The Company acknowledges and agrees that in connection with this offering, or any other services the Initial Purchasers may be deemed to be providing hereunder, notwithstanding any preexisting relationship, advisory or otherwise, between the parties or any oral representations or assurances previously or subsequently made by the Initial Purchasers: (i) no fiduciary or agency relationship between the Company, and any other person, on the one hand, and the Initial Purchasers, on the other, exists; (ii) the Initial Purchasers are not acting as advisors, expert or otherwise, to the Company, including, without limitation, with respect to the determination of the purchase price of the Securities, and such relationship between the Company, and the Initial Purchasers is entirely and solely commercial, based on arms-length negotiations; (iii) any duties and obligations that the Initial

Purchasers may have to the Company shall be limited to those duties and obligations specifically stated herein; and (iv) the Initial Purchasers and their respective affiliates may have interests that differ from those of the Company. The Company hereby waive any claims that the Company may have against the Initial Purchasers with respect to any breach of fiduciary duty in connection with the Securities.

18. *Counterparts.* This Agreement may be executed in one or more counterparts and, if executed in more than one counterpart, the executed counterparts shall each be deemed to be an original but all such counterparts shall together constitute one and the same instrument.

19. *Headings.* The headings herein are inserted for convenience of reference only and are not intended to be part of, or to affect the meaning or interpretation of, this Agreement.

If the foregoing correctly sets forth the agreement between the Company and the Initial Purchasers, please indicate your acceptance in the space provided for that purpose below.

Very truly yours,

ISIS PHARMACEUTICALS, INC.

By /s/ B. Lynne Parshall
Name: B. Lynne Parshall
Title: Executive Vice President, Chief
Financial Officer & Secretary

Accepted:

LEHMAN BROTHERS INC.
COWEN AND COMPANY, LLC
LEERINK SWANN & CO., INC
NEEDHAM & COMPANY, LLC

By LEHMAN BROTHERS INC., as *Authorized Representative*

By /s/ Tran Nguyen
Name: Tran Nguyen
Title: Vice President

SCHEDULE I

Initial Purchasers	Principal Amount of Firm Securities to be Purchased
Lehman Brothers Inc	\$ 77,500,000
Cowen and Company, LLC	37,500,000
Leerink Swann & Co., Inc.	5,250,000
Needham & Company, LLC	4,750,000
Total	\$ 125,000,000

SCHEDULE II

ISIS PHARMACEUTICALS, INC.
PRICING TERM SHEET

Initial Purchasers:

Amount (face):
Security Offered:
Issuer:
Underlying (Ticker):

Issue Price:
Coupon / YTM:
Stock Price at Pricing:
Conversion Price:
Bond Denomination:
Conversion Rate:

Maturity:

Call Feature:
Call Price Stepdown:

Puts:

1st Coupon:

Coupon Payment Dates:

Gross Spread (3.00%)
Management
Underwriting
Selling Concession

Offering Status:

144A CUSIP:
Registered CUSIP:

Trade Date:
Settlement Date:

Pot Split:

Contingent Conversion:

Contingent Interest:

Change of Control Protection:

Billing, Delivering, and Stabilizing:

Initial Purchasers' Option:

Conversion Rate Cap:

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SCHEDULE III

1. Electronic Road show slides presented to potential investors.
2. Term sheet containing the terms of the securities, substantially in the form of Schedule II.

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SCHEDULE IV

Directors

Spencer R. Berthelsen, M.D.
Stanley T. Crooke, M.D., Ph.D.
Richard D. DiMarchi
Joseph Klein
Frederick T. Muto
B. Lynne Parshall, J.D.
John C. Reed, M.D., Ph.D.
Joseph H. Wender

Officers

C. Frank Bennett, Ph.D.
David J. Ecker, Ph.D.
Arthur A. Levin, Ph.D.
Michael J. Treble
Mark K. Wedel, M.D., J.D.



**ISIS COMPLETES OFFERING OF \$125 MILLION CONVERTIBLE SUBORDINATED
NOTES TO REFINANCE EXISTING \$125 MILLION CONVERTIBLE
SUBORDINATED NOTES**

CARLSBAD, Calif., January 24, 2007 — Isis Pharmaceuticals, Inc. (NASDAQ: ISIS) announced today that it has completed the private placement of its offering of \$125 million of 2 ½% Convertible Subordinated Notes due 2027 (“New Convertible Notes”). In addition, Isis has issued an additional \$37.5 million principal amount of the New Convertible Notes pursuant to the exercise in full by the initial purchasers of their option to purchase additional New Convertible Notes.

Isis intends to use the net proceeds of this offering, which were approximately \$157.6 million, to repurchase, retire or repay its existing 5 ½% Convertible Subordinated Notes due 2009 (“Existing Convertible Notes”), of which \$125 million is currently outstanding. Through privately negotiated transactions, Isis has already agreed to repurchase approximately \$44.1 million aggregate principal amount of the total outstanding Existing Convertible Notes and plans to settle these repurchase transactions later today. In addition, the Company intends to use net proceeds remaining after such repurchase, retirement or repayment for general corporate and working capital purposes.

The New Convertible Notes were offered and sold to qualified institutional buyers pursuant to Rule 144A under the Securities Act of 1933, as amended. None of the New Convertible Notes (including any shares of common stock issuable upon conversion thereof) have been registered under the Securities Act or under any state securities laws and, unless so registered, may not be offered or sold in the United States or to U.S. persons except pursuant to an exemption from, or in a transaction not subject to the registration requirements of the Securities Act and applicable state securities laws. This press release does not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall it constitute an offer, solicitation or sale in any jurisdiction in which such offer, solicitation or sale is unlawful.

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The New Convertible Notes will be convertible under certain circumstances and redeemable in the future on terms previously disclosed.

This press release includes forward-looking statements regarding Isis Pharmaceuticals’ business and financing activities, use of proceeds from the sale of the New Convertible Notes, and plans to repurchase, retire or repay its Existing Convertible Notes. Any statement describing Isis’ goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis’ goals. Such statements are subject to certain risks and uncertainties, particularly those related to Isis’ intended use of proceeds, as well as the risks inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Isis’ forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis’ forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis’ programs are described in additional detail in Isis’ annual report on Form 10-K for the year ended December 31, 2005, and its quarterly report on Form 10-Q for the quarter ended September 30, 2006, which are on file with the SEC. Copies of these and other documents are available from Isis.

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

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Contact:

Kate Corcoran, Ph.D.
Vice President, Corporate Development

William Craumer
Executive Director, Corporate Communications

Isis Pharmaceuticals, Inc.
+1-760-603-2331