

# 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): **December 1, 2008**

### 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 December 3, 2008, Isis Pharmaceuticals, Inc. ("Isis") amended and restated its severance agreements with Stanley T. Crooke, Isis' Chief Executive Officer, and B. Lynne Parshall, Isis' Chief Financial Officer and Chief Operating Officer, to clarify the provisions of such agreements in light of Section 409A of the Internal Revenue Code.

Specifically, these severance agreements provide the following severance benefits:

- Dr. Crooke will be eligible to receive a lump sum severance payment equal to 36 months of his then-current base salary in the event his employment is terminated as a result of a change of control of Isis; and
- Ms. Parshall will be eligible to receive a lump sum severance payment equal to (i) 18 months of her then-current base salary in the event that her employment is terminated without cause and (ii) 30 months of her then-current base salary in the event that her employment is terminated as a result of a change of control of Isis.

These agreements will remain in effect as long as each individual continues to be employed by Isis.

As a condition to receiving payments under each of the retention and change of control agreements described above, the officer is required to return all of Isis' property and information and sign an agreement releasing Isis from liability.

The description of the severance agreements set forth above is qualified in its 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 5.02. Departure of Directors or Certain Officers; Election of Directors; Appointment of Certain Officers; Compensatory Arrangements of Certain Officers.

Reference is made to the information set forth in Item 1.01 above, and is incorporated herein by reference.

#### Item 5.05. Amendments to the Registrant's Code of Ethics, or Waiver of a Provision of the Code of Ethics.

The substantive updates to Isis' Code of Ethics and Business Conduct:

- specify the procedures for clearing any potential conflicts of interest under the Code of Ethics, and
- augment the previous provisions related to reporting and investigating suspected violations.

The description of Isis' Code of Ethics and Business Conduct set forth above is qualified in its entirety by reference to the full and complete terms set forth in Isis' Code of Ethics and Business Conduct, a copy of which is filed as an exhibit to this Current Report on Form 8-K and incorporated by reference herein.

**Item 9.01. Financial Statements and Exhibits.**

(d) Exhibits.

- 10.1 Amended and Restated Severance Agreement dated December 3, 2008 between Isis and Stanley T. Crooke.
- 10.2 Amended and Restated Severance Agreement dated December 3, 2008 between Isis and B. Lynne Parshall.
- 10.3 Isis' Code of Ethics and Business Conduct

**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: December 3, 2008

By: /s/ B. Lynne Parshall  
**B. LYNNE PARSHALL**  
Chief Financial Officer and Chief  
Operating Officer

**INDEX TO EXHIBITS**

- 10.1 Amended and Restated Severance Agreement dated December 3, 2008 between Isis and Stanley T. Crooke.
- 10.2 Amended and Restated Severance Agreement dated December 3, 2008 between Isis and B. Lynne Parshall.
- 10.3 Isis' Code of Ethics and Business Conduct

December 3, 2008

**VIA HAND DELIVERY**

Stanley T. Crooke  
Chairman and CEO  
Isis Pharmaceuticals, Inc.  
1896 Rutherford Road  
Carlsbad, CA 92008

Dear Stan:

As you know, in light of your contribution to Isis Pharmaceuticals, Inc. ("Isis"), Isis offered you certain severance benefits under the letter dated April 8, 2003, as amended (the "Original Agreement").

To ensure compliance with Section 409A of the Internal Revenue Code ("409A"), we now wish to amend and restate the Original Agreement with the terms of this letter agreement.

In the event that your employment is involuntarily terminated by Isis as a result of a Change in Control (as defined herein), you will be eligible to receive a lump sum severance payment equal to thirty-six (36) months of your then current base salary, less payroll deductions and withholdings.

In order to be eligible to receive the severance payment described herein, you will be required to execute an Employee Separation Agreement substantially in the form attached hereto as Exhibit A within the applicable time period set forth therein, but in no event later than forty-five (45) days following your termination. Your severance payment will be due and payable on or before the fifth (5<sup>th</sup>) business day following the effective date of the Employee Separation Agreement.

For purposes of this letter agreement, Change in Control will be defined as follows: (i) a sale of all or substantially all of the assets of Isis; (ii) a merger or consolidation in which Isis is not the surviving corporation and in which beneficial ownership of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; (iii) a reverse merger in which Isis is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise, and in which beneficial ownership of securities of Isis representing at least fifty percent (50%) of the

---

combined voting power entitled to vote in the election of Directors has changed; or (iv) an acquisition by any person, entity or group within the meaning of Section 13(d) or 14(d) of the Exchange Act, or any comparable successor provisions (excluding any employee benefit plan, or related trust, sponsored or maintained by Isis or subsidiary of Isis or other entity controlled by Isis) of the beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act, or comparable successor rule) of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors.

Notwithstanding the foregoing, you will only be entitled to receive the severance payment if the termination of your employment constitutes a "separation from service" (as such term is defined in Treasury Regulation Section 1.409A-1(h)). For the avoidance of doubt, it is intended that the severance payment satisfy the exemption from the application of Section 409A provided under Treasury Regulation Section 1.409A-1(b)(4).

Please keep in mind that this letter agreement is not intended to change your status as an at-will employee with Isis. As with all employees at Isis, you or Isis may terminate your employment at any time, for any reason whatsoever, with or without cause or advance notice subject to the provisions set forth herein.

If you have any questions or comments regarding the terms and conditions of this letter, please do not hesitate to contact me.

Very truly yours,

Isis Pharmaceuticals, Inc.

/s/ Spencer R. Berthelsen, M.D.  
Spencer R. Berthelsen, M.D.  
Chairman of the Compensation Committee

**Acknowledged and Agreed:**

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

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

This **SEPARATION AGREEMENT** (“Agreement”) is made and entered into by and between (“Employee”) and (“the Company”) as of the Effective Date of this Agreement, as defined in paragraph 10 below.

**WHEREAS**, the Company wishes to provide Employee with certain benefits in consideration of Employee’s service to the Company and the promises and covenants of Employee as contained herein;

**NOW, THEREFORE**, in consideration of the mutual promises and covenants contained herein, it is hereby agreed by and between the parties hereto as follows:

1. **SEVERANCE PAYMENTS.** On (“Separation Date”), Employee shall cease to be an employee or officer of the Company for all purposes. In return for executing this Agreement, Employee will receive a lump sum severance payment equal to thirty-six (36) months of your then current base salary, less payroll deductions and withholdings. This severance payment will be due and payable on or before the fifth (5<sup>th</sup>) business day following the Effective Date.
2. **ACCRUED SALARY AND PAID TIME OFF.** On or about the Separation Date, the Company will pay Employee all accrued salary, and all accrued and unused vacation, subject to standard payroll deductions and withholdings. Employee is entitled to these payments regardless of whether or not Employee signs this Agreement.
3. **EMPLOYMENT SEARCH SUPPORT.** Commencing on the Separation Date, the Company will provide Employee offsite employment search support through Right Management Associates as outlined in Exhibit A attached hereto.
4. **HEALTH INSURANCE.** To the extent permitted by law and by the Company’s current group health insurance policies, after the Separation Date, Employee will be eligible to continue receiving health insurance benefits under the federal or state COBRA law at Employee’s own expense and later to convert to an individual policy if desired. Employee will be provided with a separate notice regarding COBRA benefits. If Employee elects continued coverage under COBRA, the Company will reimburse Employee’s COBRA premiums for one (1) month as part of this Agreement. In addition, to the extent permitted by law and by the Company’s current vision and dental insurance policies, after the Separation Date, the Company will reimburse Employee’s vision and dental benefit premiums for one (1) month.
5. **STOCK OPTIONS.** Pursuant to the Company’s 199\_ Equity Incentive Plan (the “Plan”) and Employee’s Stock Option Agreement (a copy of which is attached hereto as Exhibit B), vesting of Employee’s stock options will cease on the Separation Date. Employee’s rights to exercise Employee’s option as to any vested shares will be as set forth in the Plan and Employee’s Stock Option Agreement.

---

6. **OTHER BENEFITS.** Except as expressly provided herein, Employee acknowledges that Employee will not receive (nor is entitled to receive) any additional compensation or benefits.

7. **RETURN OF COMPANY PROPERTY.** By three (3) days after the Separation Date, Employee will return to the Company all Company documents (and all copies thereof) and other Company property and materials in Employee’s possession, or control, including, but not limited to, Company files, notes, memoranda, correspondence, lists, drawings, records, plans and forecasts, financial information, personnel information, customer and customer prospect information, sales and marketing information, product development and pricing information, specifications, computer-recorded information, tangible property, equipment, credit cards, entry cards, identification badges and keys; and any materials of any kind which contain or embody any proprietary or confidential information of the Company (and all reproductions thereof).

8. **PROPRIETARY INFORMATION OBLIGATIONS.** Employee acknowledges that nothing herein shall impair the covenants and obligations set forth in Employee’s Proprietary Information and Inventions Agreement, a copy of which is attached hereto as Exhibit C.

9. **EMPLOYEE’S RELEASE OF CLAIMS.** Except as otherwise set forth in this Agreement, in exchange for consideration under this Agreement to which Employee would not otherwise be entitled, Employee hereby releases, acquits and forever discharges the Company, its parents and subsidiaries, and their officers, directors, agents, servants, employees, attorneys, shareholders, successors, assigns and affiliates, of and from any and all claims, liabilities, demands, causes of action, costs, expenses, attorneys fees, damages, indemnities and obligations of every kind and nature, in law, equity, or otherwise, known and unknown, suspected and unsuspected, disclosed and undisclosed, arising out of or in any way related to agreements, events, acts or conduct at any time prior to and including the execution date of this Agreement, including but not limited to: all such claims and demands directly or indirectly arising out of or in any way connected with Employee’s employment with the Company or the termination of that employment; claims or demands related to salary, bonuses, commissions, stock, stock options, or any other ownership interests in the Company, vacation pay, fringe benefits, expense reimbursements, severance pay, or any other form of compensation; claims pursuant to any federal, state or local law, statute, or cause of action including, but not limited to, the federal Civil Rights Act of 1964, as amended; the federal Americans with Disabilities Act of 1990; the federal Age Discrimination in Employment Act of 1967, as amended (“ADEA”); the California Fair Employment and Housing Act, as amended; tort law; contract law; wrongful discharge; discrimination; harassment; fraud; defamation; emotional distress; and breach of the implied covenant of good faith and fair dealing.

10. **ADEA WAIVER.** Employee acknowledges that Employee knowingly and voluntarily waives and releases any rights Employee may have under the ADEA, as amended. Employee also acknowledges that the consideration given for the waiver and release in the preceding paragraph hereof is in addition to anything of value to which Employee was already entitled. Employee further acknowledges that Employee has been advised by this writing, as required by the ADEA, that: (a) Employee’s waiver and release do not apply to any rights or claims that may arise after the execution date of this Agreement; (b) Employee has the right to consult with an attorney prior to executing this Agreement; (c) Employee has forty-five (45) days

---

to consider this Agreement (although Employee may choose to voluntarily execute this Agreement earlier); (d) Employee has seven (7) days following the execution of this Agreement by the parties to revoke the Agreement; and (e) this Agreement shall not be effective until the date upon which the revocation period has expired, which shall be the eighth day after this Agreement is executed by Employee, provided that the Company has also executed this Agreement by that date (“Effective Date”).

11. **SECTION 1542 WAIVER.** Employee acknowledges reading and understanding Section 1542 of the Civil Code of the State of California:

**A general release does not extend to claims which the creditor does not know or suspect to exist in his favor at the time of executing the release, which if known by him must have materially affected his settlement with the debtor.**

Employee hereby expressly waives and relinquishes all rights and benefits under that section and any law or legal principle of similar effect in any jurisdiction with respect to the release of unknown and unsuspected claims granted in this Agreement.

12. **ARBITRATION.** To ensure rapid and economical resolution of any and all disputes that may arise in connection with the Agreement, the parties agree that any and all disputes, claims, causes of action, in law or equity, arising from or relating to this Agreement or its enforcement, performance, breach, or interpretation, with the sole exception of those disputes that may arise from Employee's Proprietary Information and Inventions Agreement, will be resolved by final and binding confidential arbitration held in San Diego, California and conducted by the American Arbitration Association ("AAA") under its then-existing Rules and Procedures. Nothing in this paragraph is intended to prevent either party from obtaining injunctive relief in court to prevent irreparable harm pending the conclusion of any such arbitration.

13. **ENTIRE AGREEMENT.** This Agreement, including all exhibits, constitutes the complete, final and exclusive embodiment of the entire agreement between Employee and the Company with regard to the subject matter hereof. It supersedes any and all agreements entered into by and between Employee and the Company where such other agreement may conflict with this agreement. It is entered into without reliance on any promise or representation, written or oral, other than those expressly contained herein. It may not be modified except in a writing signed by Employee and a duly authorized officer of the Company. The parties have carefully read this Agreement, have been afforded the opportunity to be advised of its meaning and consequences by their respective attorneys, and signed the same of their own free will.

14. **MISCELLANEOUS.** This Agreement shall bind the heirs, personal representatives, successors, assigns, executors and administrators of each party, and inure to the benefit of each party, its heirs, successors and assigns. This Agreement shall be deemed to have been entered into and shall be construed and enforced in accordance with the laws of the State of California as applied to contracts made and to be performed entirely within California. If an arbitrator or court of competent jurisdiction determines that any term or provision of this Agreement is invalid or unenforceable, in whole or in part, then the remaining terms and provisions hereof shall be unimpaired, the invalid or unenforceable term or provision shall be modified or replaced so as to render it valid and enforceable in a manner which represents the

---

parties' intention with respect to the invalid or unenforceable term or provision insofar as possible. This Agreement may be executed in two counterparts, each of which shall be deemed an original, all of which together shall constitute one and the same instrument.

**IN WITNESS WHEREOF,** the parties have duly authorized and caused this Agreement to be executed as follows:

**EMPLOYEE**

\_\_\_\_\_

By: \_\_\_\_\_

---

December 3, 2008

**VIA HAND DELIVERY**

B. Lynne Parshall  
COO and CFO  
Isis Pharmaceuticals, Inc.  
1896 Rutherford Road  
Carlsbad, CA 92008

Dear Lynne:

As you know, in light of your contribution to Isis Pharmaceuticals, Inc. ("Isis"), Isis offered you certain severance benefits under the letter dated April 8, 2003, as amended (the "Original Agreement").

To ensure compliance with Section 409A of the Internal Revenue Code ("409A"), we now wish to amend and restate the Original Agreement with the terms of this letter agreement.

In the event that your employment is involuntarily terminated without "cause" (as defined herein) by Isis, you will be eligible to receive a lump sum severance payment equal to eighteen (18) months of your then current base salary, less payroll deductions and withholdings. For purposes of this letter agreement, "cause" will be defined as follows: (i) engaging or in any manner participating in any activity which is competitive with or intentionally injurious to Isis or which violates any provision of the Proprietary Information and Inventions Agreement; (ii) commission of any fraud against Isis or use or appropriation for personal use or benefit of any funds or properties of Isis not authorized by the Isis to be so used or appropriated; (iii) conviction of a crime involving dishonesty or moral turpitude; (iv) conduct by you which in the good faith and reasonable determination of Isis demonstrates gross unfitness to serve in your then current capacity at Isis.

However, if your employment is involuntarily terminated by Isis as a result of a Change in Control (as defined herein), instead of the 18-month payment described above, you will be eligible to receive a lump sum severance payment equal to thirty (30) months of your then current base salary, less payroll deductions and withholdings.

In order to be eligible to receive the severance payment described herein, you will be required to execute an Employee Separation Agreement substantially in the form attached hereto as Exhibit A within the applicable time period set forth therein, but in no event

---

later than forty-five (45) days following your termination. Your severance payment will be due and payable on or before the fifth (5<sup>th</sup>) business day following the effective date of the Employee Separation Agreement.

For purposes of this letter agreement, Change in Control will be defined as follows: (i) a sale of all or substantially all of the assets of Isis; (ii) a merger or consolidation in which Isis is not the surviving corporation and in which beneficial ownership of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; (iii) a reverse merger in which Isis is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise, and in which beneficial ownership of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors has changed; or (iv) an acquisition by any person, entity or group within the meaning of Section 13(d) or 14(d) of the Exchange Act, or any comparable successor provisions (excluding any employee benefit plan, or related trust, sponsored or maintained by Isis or subsidiary of Isis or other entity controlled by Isis) of the beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act, or comparable successor rule) of securities of Isis representing at least fifty percent (50%) of the combined voting power entitled to vote in the election of Directors.

Notwithstanding the foregoing, you will only be entitled to receive the severance payment if the termination of your employment constitutes a "separation from service" (as such term is defined in Treasury Regulation Section 1.409A-1(h)). For the avoidance of doubt, it is intended that the severance payment satisfy the exemption from the application of Section 409A provided under Treasury Regulation Section 1.409A-1(b)(4).

Please keep in mind that this letter agreement is not intended to change your status as an at-will employee with Isis. As with all employees at Isis, you or Isis may terminate your employment at any time, for any reason whatsoever, with or without cause or advance notice subject to the provisions set forth herein.

If you have any questions or comments regarding the terms and conditions of this letter, please do not hesitate to contact me.

Very truly yours,

Isis Pharmaceuticals, Inc.

---

/s/ Spencer R. Berthelsen, M.D.

/s/ Spencer R. Berthelsen, M.D.

Chairman of the Compensation Committee

**Acknowledged and Agreed:**

B. Lynne Parshall

---

**EXHIBIT A  
SEPARATION AGREEMENT**

This **SEPARATION AGREEMENT** ("Agreement") is made and entered into by and between \_\_\_\_\_ ("Employee") and ("the Company") as of the Effective Date of this Agreement, as defined in paragraph 10 below.

**WHEREAS**, the Company wishes to provide Employee with certain benefits in consideration of Employee's service to the Company and the promises and covenants of Employee as contained herein;

**NOW, THEREFORE**, in consideration of the mutual promises and covenants contained herein, it is hereby agreed by and between the parties hereto as follows:

1. **SEVERANCE PAYMENTS.** On \_\_\_\_\_ ("Separation Date"), Employee shall cease to be an employee or officer of the Company for all purposes. In return for executing this Agreement, Employee will receive a lump sum severance payment equal to [ ] months of your then current base salary, less payroll deductions and withholdings. This severance payment will be due and payable on or before the fifth (5<sup>th</sup>) business day following the Effective Date.
  2. **ACCRUED SALARY AND PAID TIME OFF.** On or about the Separation Date, the Company will pay Employee all accrued salary, and all accrued and unused vacation, subject to standard payroll deductions and withholdings. Employee is entitled to these payments regardless of whether or not Employee signs this Agreement.
  3. **EMPLOYMENT SEARCH SUPPORT.** Commencing on the Separation Date, the Company will provide Employee offsite employment search support through Right Management Associates as outlined in Exhibit A attached hereto.
  4. **HEALTH INSURANCE.** To the extent permitted by law and by the Company's current group health insurance policies, after the Separation Date, Employee will be eligible to continue receiving health insurance benefits under the federal or state COBRA law at Employee's own expense and later to convert to an individual policy if desired. Employee will be provided with a separate notice regarding COBRA benefits. If Employee elects continued coverage under COBRA, the Company will reimburse Employee's COBRA premiums for one (1) month as part of this Agreement. In addition, to the extent permitted by law and by the Company's current vision and dental insurance policies, after the Separation Date, the Company will reimburse Employee's vision and dental benefit premiums for one (1) month.
  5. **STOCK OPTIONS.** Pursuant to the Company's 199\_ Equity Incentive Plan (the "Plan") and Employee's Stock Option Agreement (a copy of which is attached hereto as Exhibit B), vesting of Employee's stock options will cease on the Separation Date. Employee's rights to exercise Employee's option as to any vested shares will be as set forth in the Plan and Employee's Stock Option Agreement.
- 
6. **OTHER BENEFITS.** Except as expressly provided herein, Employee acknowledges that Employee will not receive (nor is entitled to receive) any additional compensation or benefits.
  7. **RETURN OF COMPANY PROPERTY.** By three (3) days after the Separation Date, Employee will return to the Company all Company documents (and all copies thereof) and other Company property and materials in Employee's possession, or control, including, but not limited to, Company files, notes, memoranda, correspondence, lists, drawings, records, plans and forecasts, financial information, personnel information, customer and customer prospect information, sales and marketing information, product development and pricing information, specifications, computer-recorded information, tangible property, equipment, credit cards, entry cards, identification badges and keys; and any materials of any kind which contain or embody any proprietary or confidential information of the Company (and all reproductions thereof).
  8. **PROPRIETARY INFORMATION OBLIGATIONS.** Employee acknowledges that nothing herein shall impair the covenants and obligations set forth in Employee's Proprietary Information and Inventions Agreement, a copy of which is attached hereto as Exhibit C.
  9. **EMPLOYEE'S RELEASE OF CLAIMS.** Except as otherwise set forth in this Agreement, in exchange for consideration under this Agreement to which Employee would not otherwise be entitled, Employee hereby releases, acquits and forever discharges the Company, its parents and subsidiaries, and their officers, directors, agents, servants, employees, attorneys, shareholders, successors, assigns and affiliates, of and from any and all claims, liabilities, demands, causes of action, costs, expenses, attorneys fees, damages, indemnities and obligations of every kind and nature, in law, equity, or otherwise, known and unknown, suspected and unsuspected, disclosed and undisclosed, arising out of or in any way related to agreements, events, acts or conduct at any time prior to and including the execution date of this Agreement, including but not limited to: all such claims and demands directly or indirectly arising out of or in any way connected with Employee's employment with the Company or the termination of that employment; claims or demands related to salary, bonuses, commissions, stock, stock options, or any other ownership interests in the Company, vacation pay, fringe benefits, expense reimbursements, severance pay, or any other form of compensation; claims pursuant to any federal, state or local law, statute, or cause of action including, but not limited to, the federal Civil Rights Act of 1964, as amended; the federal Americans with Disabilities Act of 1990; the federal Age Discrimination in Employment Act of 1967, as amended ("ADEA"); the California Fair Employment and Housing Act, as amended; tort law; contract law; wrongful discharge; discrimination; harassment; fraud; defamation; emotional distress; and breach of the implied covenant of good faith and fair dealing.
  10. **ADEA WAIVER.** Employee acknowledges that Employee knowingly and voluntarily waives and releases any rights Employee may have under the ADEA, as amended. Employee also acknowledges that the consideration given for the waiver and release in the preceding paragraph hereof is in addition to anything of value to which Employee was already entitled. Employee further acknowledges that Employee has been advised by this writing, as

required by the ADEA, that: (a) Employee's waiver and release do not apply to any rights or claims that may arise after the execution date of this Agreement; (b) Employee has the right to consult with an attorney prior to executing this Agreement; (c) Employee has forty-five (45) days

---

to consider this Agreement (although Employee may choose to voluntarily execute this Agreement earlier); (d) Employee has seven (7) days following the execution of this Agreement by the parties to revoke the Agreement; and (e) this Agreement shall not be effective until the date upon which the revocation period has expired, which shall be the eighth day after this Agreement is executed by Employee, provided that the Company has also executed this Agreement by that date ("Effective Date").

11. **SECTION 1542 WAIVER.** Employee acknowledges reading and understanding Section 1542 of the Civil Code of the State of California:

**A general release does not extend to claims which the creditor does not know or suspect to exist in his favor at the time of executing the release, which if known by him must have materially affected his settlement with the debtor.**

Employee hereby expressly waives and relinquishes all rights and benefits under that section and any law or legal principle of similar effect in any jurisdiction with respect to the release of unknown and unsuspected claims granted in this Agreement.

12. **ARBITRATION.** To ensure rapid and economical resolution of any and all disputes that may arise in connection with the Agreement, the parties agree that any and all disputes, claims, causes of action, in law or equity, arising from or relating to this Agreement or its enforcement, performance, breach, or interpretation, with the sole exception of those disputes that may arise from Employee's Proprietary Information and Inventions Agreement, will be resolved by final and binding confidential arbitration held in San Diego, California and conducted by the American Arbitration Association ("AAA") under its then-existing Rules and Procedures. Nothing in this paragraph is intended to prevent either party from obtaining injunctive relief in court to prevent irreparable harm pending the conclusion of any such arbitration.

13. **ENTIRE AGREEMENT.** This Agreement, including all exhibits, constitutes the complete, final and exclusive embodiment of the entire agreement between Employee and the Company with regard to the subject matter hereof. It supersedes any and all agreements entered into by and between Employee and the Company where such other agreement may conflict with this agreement. It is entered into without reliance on any promise or representation, written or oral, other than those expressly contained herein. It may not be modified except in a writing signed by Employee and a duly authorized officer of the Company. The parties have carefully read this Agreement, have been afforded the opportunity to be advised of its meaning and consequences by their respective attorneys, and signed the same of their own free will.

14. **MISCELLANEOUS.** This Agreement shall bind the heirs, personal representatives, successors, assigns, executors and administrators of each party, and inure to the benefit of each party, its heirs, successors and assigns. This Agreement shall be deemed to have been entered into and shall be construed and enforced in accordance with the laws of the State of California as applied to contracts made and to be performed entirely within California. If an arbitrator or court of competent jurisdiction determines that any term or provision of this Agreement is invalid or unenforceable, in whole or in part, then the remaining terms and provisions hereof shall be unimpaired, the invalid or unenforceable term or provision shall be modified or replaced so as to render it valid and enforceable in a manner which represents the

---

parties' intention with respect to the invalid or unenforceable term or provision insofar as possible. This Agreement may be executed in two counterparts, each of which shall be deemed an original, all of which together shall constitute one and the same instrument.

**IN WITNESS WHEREOF,** the parties have duly authorized and caused this Agreement to be executed as follows:

**EMPLOYEE**

\_\_\_\_\_

By: \_\_\_\_\_

---



**Section VII.**

Isis Policy and Procedures Manual

**CODE OF ETHICS AND BUSINESS CONDUCT**

*Reviewed & Approved – 12/2008*  
*Next Review – 12/2009 March 2008*  
*Document Owner – LegalCFO*

ISIS PHARMACEUTICALS, INC.  
 1896 Rutherford Road  
 Carlsbad, CA 92008

1

**Code of Ethics and Business Conduct**  
**Table of Contents**

<b>SECTION VII. CODE OF ETHICS AND BUSINESS CONDUCT</b>	<b>1</b>
PHILOSOPHY OF ISIS CODE OF ETHICS AND BUSINESS CONDUCT	3
COMPLIANCE WITH LAWS AND REGULATIONS	3
ETHICAL CONDUCT	3
YOUR RESPONSIBILITY	3
BUSINESS PRACTICES	4
Interaction with Competitors	4
Bribes, Kickbacks and Similar Payments	4
Books, Records and Information Management	4
Retention of Records	5
Audit Integrity	5
CONFLICTS OF INTEREST	5
PRE-CLEARANCE PROCEDURE	5
CERTAIN PRE-CLEARED BUSINESS ACTIVITIES	6
DISHONESTY AND THEFT	6
INSIDER TRADING	6
WAIVERS FOR EXECUTIVE OFFICERS AND DIRECTORS	7
REPORTING SUSPECTED VIOLATIONS	7
CONSEQUENCES OF VIOLATING ISIS' CODE OF ETHICS	8
APPENDIX A – The Foreign Corrupt Practices Act	9

2

## PHILOSOPHY OF ISIS CODE OF ETHICS AND BUSINESS CONDUCT

*Approved – Drafting*  
*Next Review – 12/07*  
*Document Owner – COO*

Isis Pharmaceuticals, Inc. (hereinafter referred to as “Isis” or the “Company”) will adhere to high legal and ethical standards. As such, this Code of Ethics and Business Conduct (hereinafter referred to as the “Code of Ethics”) applies to each of Isis’ employees (including its executive officers) and each member of the Isis Board of Directors.

## COMPLIANCE WITH LAWS AND REGULATIONS

*Approved –*  
*Next Review –*  
*Document Owner –*

As a U.S. company, Isis is governed by and required to comply with U.S. federal law. In addition to complying with federal law, Isis will conduct all its activities in compliance with all applicable national, state and local laws, regulations and judicial decrees wherever it conducts business.

At no time will you take any action on behalf of the Company that you know, or reasonably should know, violates any law or regulation. Whenever possible, you will strive to comply with the spirit of the law as well as its letter.

No code of conduct can cover all circumstances or anticipate every situation. When you encounter situations not addressed specifically by this Code of Ethics, you should apply its overall philosophy and concepts to the situation. You should also refer to specific Company policies on the subject in question or similar subjects. If you still have a question about the appropriateness of an action, you should review the particular circumstances with Isis’ COO Executive Vice President, CEO or the Audit Committee of the Board of Directors.

Approved –  
Next Review –  
Document Owner –

You should strive to act in a manner using good judgment, high ethical standards and honesty in your business dealings on behalf of the Company. Unethical practices and activities do not serve the interests of the Company or the community, even if they do not technically violate the law.

Your Responsibilities

- Know and comply with the Isis Code of Ethics and Company policies that apply to business activities.
- Be honest, fair and trustworthy in all business activities and relationships.
- Provide and support a culture that values integrity and ethical conduct.
- Avoid all conflicts of interest between work and personal affairs.
- Report suspected violations of law, the Isis Code of Ethics or Company Policies.
- Cooperate in any investigation into possible violations of law, the Isis Code of Ethics or Company Policies.

Business Practices

It is Isis' policy to deal with its business associates, partners, suppliers, competitors and any governments or governmental agencies with which it interacts in an ethical manner. As such, you will comply with the principles outlined below and will take steps to ensure similar compliance by the persons you directly manage.

Interaction with Competitors

As a vigorous competitor in the marketplace, Isis will seek economic knowledge about our competitors. However, you will not engage in illegal or improper acts to acquire any competitor information. In addition, you will not hire competitors' employees for the purpose of obtaining confidential information, urge competitors' personnel, customers or suppliers to disclose confidential information, or seek such information from competitors' employees subsequently hired by the Company.

Bribes, Kickbacks and Similar Payments

You are prohibited from paying or receiving any bribe, kickback or other similar payment to or from any public official, or government, or other individual, to secure any concession, contract or other favorable treatment for Isis or you. This prohibition extends to the payment or receipt of money or anything else of substantial value when you have reason to believe that some part of the payment or "fee" will be used for a bribe, kickback or other similar activity.

Because Isis is a global company and does business worldwide, you must comply with the United States Foreign Corrupt Practices Act of 1977. For more detail, please read a definition of the "Foreign Corrupt Practices Act," attached as Appendix A.

Books, Records and Information Management

Isis' books of account and records must be accurately maintained and fully disclose the nature of transactions reflected in them. Penalties for violating the laws and regulations in this area could be severe for the Company and the employees involved. Isis will maintain these books according to the following record-keeping requirements and in compliance with the spirit and letter of applicable laws and regulations:

- All books, records and accounts must be kept in reasonable detail and must accurately and fairly reflect all transactions and dispositions of the Company's assets.
- All disbursements of funds and all receipts must be properly and promptly recorded.
- No undisclosed or unrecorded fund or account may be established for any purposes.
- False or artificial entries must never be made in any of the books or records of the Company, or in any public record for any reason, nor should the Company's records be falsely altered in any way.

You will not take any action, for the purpose of rendering the Company's financial statements materially misleading, or to fraudulently influence, coerce, manipulate, or mislead any independent accountant engaged in the performance of an audit of the Company's financial statements.

Retention of Records

Legal practice requires the retention of certain records for various periods of time, particularly those relating to taxes, personnel, contracts and corporate structure. When litigation or a government investigation or audit is pending or imminent, you must not destroy any relevant records until the matter is closed. Destruction of records to avoid disclosure in a legal proceeding or investigation may constitute a criminal offense.

#### Audit Integrity

No officer or director of Isis, or any other person acting under their direction, will take any action to fraudulently influence, coerce, manipulate, or mislead any independent accountant engaged in the performance of an audit of the Company's financial statements for the purpose of rendering the Company's financial statements materially misleading.

#### Conflicts of Interest

As an employee you cannot without the Company's express written consent, engage in any employment or business activity other than for the Company. Unless expressly consented to in writing by the Company, your personal activities should not involve the use of Company property, facilities, influence or other resources, and should not reflect discredit upon the Company.

You will not engage in any activity through which you stand to benefit personally from any sale or purchase of goods and services by the Company. This provision does not apply to benefits arising out of your employment with the Company, or to ownership of equity in a publicly traded company which was purchased on the open market and represents (i) less than 1% of such company's outstanding equity and (ii) less than 5% of your equity portfolio.

You must promptly disclose in writing any actual or potential conflicts of interest to Isis' COO, CEO or General Counsel. Isis will review the matter, as set forth above, and communicate its position in writing.

#### Pre-Clearance Procedure

All employees must pre-clear any employment or business activity other than for the Company. To do so, you should contact either (i) the CEO, (ii) COO or (iii) General Counsel and explain to them the proposed business activity you wish to engage in. If you are an executive officer, the Nominating, Governance and Review Committee will evaluate the proposed business activity and will notify you whether such activity has been approved. For all other employees, the CEO or COO will evaluate the proposed business activity and will notify you whether such activity has been approved. In some cases, the individual(s) reviewing your request may discuss your request with other members of the Isis management team. Remember, just because you have to pre-clear a certain activity, does not mean that Isis will prevent you doing it.

Members of the Board of Directors must request and receive Without a determination from the Board of Directors (for executive officers and Directors) or the CEO or Executive Vice President (for non-executive officers) that no conflict from the Nominating, Governance and Review Committee before engaging in of interest exists, you will not engage in any activity, including acting as an employee or , director, or advisor for any entity that directly or indirectly competes with Isis.

#### Certain Pre-Cleared Business Activities

Isis' management has already pre-cleared certain business activities that should not cause a conflict of interest. For these activities, employees generally do not need to obtain written permission from the Company. However, please use your common sense because even with pre-cleared activities, conflicts of interest can arise. If you are ever in doubt, you should follow the pre-clearance procedures outlined above. The pre-cleared business activities include:

- Working in the food service or hospitality industry after normal business hours;
- Owning rental property (unless Isis rents the property);
- Philanthropic or pro bono activities;
- Farming;
- Home-based retail (e.g. Amway, Tupperware, cosmetics), provided you do not solicit sales during Isis business hours or at the Isis workplace; and
- Fitness instructor.

You must promptly disclose in writing any actual or potential conflicts of interest to Isis' Executive Vice President, CEO or Vice President Human Resources. Isis will review the matter, as set forth above, and communicate its position in writing.

#### Dishonesty and Theft

You will not knowingly:

- Engage in fraud or embezzlement affecting Company property, funds, securities or other assets; or
- Willfully damage or destroy property or materials belonging to the Company, its employees or customers.

In addition, without proper supervisory authorization, you will not knowingly:

- Remove property, material or money from the Company, its employees, or its customers for personal gain, personal use, resale or to give to another party;
- Receive property, materials or money belonging to the Company, its employees or its customers for personal gain, personal use, resale or to give to another party;
- Access, remove, publish, destroy or alter private or confidential information existing in physical Company records or electronically stored information;

- Remove, publish, destroy or alter other physical Company records or electronically stored information affecting the Company, its employees or corporate partners; or
- Copy, reprint, duplicate, or recreate in whole or in part, computer programs or related systems developed or modified by Isis personnel, or acquired from outside vendors.

### Insider Trading

During the course of your employment, you may receive important information which is not yet publicly available (“inside information”) about Isis or about other publicly traded companies with which the Company has business dealings. Because of your access to this information, you may be in a position to profit financially by buying or selling or in some other way dealing in Company stock or the stock of another publicly traded company. Similarly, Or you may be in a position to benefit financially or

6

---

otherwise by passing this information on to some other person. Whether you personally benefit or another benefits, this is considered “insider trading” and is illegal.

You may not disclose inside information to anyone inside the Company who is not authorized to access it or to anyone outside the Company. When you have access to inside information, you may not buy or sell Isis stock regardless of the number of shares nor may you encourage or discourage others from trading on Company stock.

### WAIVERS FOR EXECUTIVE OFFICERS AND DIRECTORS

Any waiver of this Code of Ethics for executive officers or members of the Board of Directors must be approved by the Nominating, Governance and Review Committee Board of Directors and must be promptly disclosed to the Company’s stockholders, including the reasons for the waiver.

### REPORTING SUSPECTED VIOLATIONS

Isis is committed to complying with all applicable securities laws and to filing fair and accurate disclosures with the SEC. Each Employee who reports suspected If you suspect accounting improprieties or , violations of the law or this Code of Ethics or of any laws specifically including federal mail fraud, wire fraud, or securities fraud statutes will be taken seriously and the allegations will be thoroughly investigated.

An employee who suspects accounting improprieties or violations of this Code of Ethics or of any laws specifically including federal mail fraud, wire fraud, or securities fraud statutes should take the following steps:

1. The employee you should immediately communicate his/heryour concern to the Vice President Human Resources, the General Counsel, the COO Executive Vice President or the CEO. To ensure the highest quality response, employees should communicate directly with Any one of these designated Isis officials. However, any concern may be made anonymously and will be taken seriously.
2. Any officer receivingofficers who receives such a complaint will immediately communicate the complaint to the chairman of the Audit Committee or. Alternatively, you may directly report a suspected violation any such violations directly to the Chairmanchairman of the Audit Committee.
3. The Audit Committee together with management will conduct, if appropriate, a confidential, but not anonymous investigation which will involve talking to the complainant (if known), the accused, and as circumstances warrant, any witnesses, and anyone who may have similar complaints.
4. Any concern may be made anonymously and will be taken seriously. All parties involved in the investigation will be required to cooperate fully, maintain complete confidentiality and take no action which might be considered retaliatory.
5. Once the investigation is complete, the Audit Committee will make a determination as to what happened, the level of severity and the appropriate remedial action, and will take such action.

Isis will not discharge, demote, suspend, threaten, harass, or in any other manner discriminate against an employee because you (1) have provided information, caused information to be

7

---

provided, or otherwise assisted in an investigation regarding any conduct which you reasonably believe constitutes a violation of this Code of Ethics or of the federal mail fraud, wire fraud, or securities fraud statutes, any SEC rule or any provision of federal law relating to fraud against stockholders, when the information or assistance is provided to or the investigation is conducted by a federal regulatory or law enforcement agency, any Member of Congress or Congressional committee, or a person with supervisory authority over the employee or (2) have filed, caused to be filed, testified, participated in or otherwise assisted in a proceeding filed or about to be filed (with any knowledge of Isis) relating to an alleged violation of the federal mail fraud, wire fraud, or securities fraud statutes, any SEC rule or any provision of federal law relating to fraud against stockholders. An employee who alleges such discharge or discrimination may file a civil complaint with the Secretary of Labor.

### CONSEQUENCES OF VIOLATING ISIS’ CODE OF ETHICS

If you violate the law, the Isis Code of Ethics or Isis’ policies, you may be subject to disciplinary action, up to and including termination. If necessary, Isis may suspend your employment during an investigation into an alleged breach. Additional actions may include reassignment of work duties and limitation in future job opportunities. Isis may refer violations of law to local or federal law enforcement authorities for possible prosecution.

8

### The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act (FCPA) prohibits U.S. companies from making improper payments or gifts to foreign officials. Company policy requires that all directors, officers, employees, agents and consultants of Isis comply with the FCPA.

A. Definition of Foreign Official

Under the FCPA, the term “foreign official” includes elected and appointed governmental officials, candidates for public office, foreign political parties, officers and employees of government owned or controlled enterprises, and public international organizations. When in doubt, Isis employees should consult the Company’s Legal Counsel for advice on whether a potential recipient of a payment is a “foreign official.”

B. Prohibited Acts

The following acts are prohibited by the FCPA:

1. Authorizing, paying, promising or delivering any payment, gift or favor intended to influence any foreign official on a matter within that person’s responsibilities. For example, any payment to any foreign official for the purposes of obtaining or retaining sales of products or services to Isis, sales by Isis of Isis products or services, to win a bid or contract, or to obtain more favorable tax treatment is prohibited.
2. Any indirect payment to a third party if the payor knows that the third party may make a prohibited payment. For example, any payment to an Isis agent or consultant where the payor is aware or has firm belief that such agent or consultant may make an improper payment to a foreign official is prohibited. The Isis payor may not avoid this prohibition by deliberately ignoring or purposefully avoiding knowledge that a bribe may be paid.
3. Establishing any undisclosed or unrecorded “slush” funds or assets; making any false or artificial entries in company books or records; failing to keep books, records and accounts in reasonable detail to reflect accurately the handling of money and other assets; and failing to maintain internal accounting controls sufficient to verify that no improper payments have been made.

9

---

C. Permissible Payments

The following payments may be made:

1. Payments to a foreign official for the purpose of expediting or securing the performance of a routine governmental action. Payments for the following routine governmental actions are permissible: obtaining permits, licenses or other official documents to qualify to do business in a foreign country; processing governmental papers, such as visas and work orders; assuring police protection, mail pickup and delivery, or scheduling inspections associated with contract performance or inspections related to the transit of goods across country; and providing phone service, power and water supply, loading and unloading cargo or protecting perishable products or commodities from deterioration. Routine governmental action does not include any decision by a foreign official to encourage, to award, to continue or to modify the terms relating to any business with any Isis entity.
2. Any payment that is lawful under the written laws and regulations of the foreign country.
3. Any reasonable expenditure directly related to the promotion, demonstration or explanation of Isis products or services or the execution or performance of a contract with a foreign government or agency, such as the travel and lodging expenses of a foreign official on a trip for such purposes.

D. Penalties

Violations of the anti-bribery provisions of the FCPA may result in criminal fines of up to \$2,000,000 for corporations and \$100,000 and five years imprisonment for individuals. Violations of the accounting provisions may result in fines of up to \$2,500,000 for corporations and \$1,000,000 and ten years imprisonment for individuals. Under alternative fine provisions, a violator may be fined up to twice the amount of the gain or loss resulting from a violation.

Payments and the FCPA

Neither Isis nor any director, officer, employee, agent or consultant of the Company will directly or indirectly make or promise illegal payments or contributions, or engage in any other illegal conduct in order to influence customers, suppliers or governmental entities, including their officials or employees, to secure or retain business, to encourage any such employees or officials to fail to perform or to perform improperly their official functions or to influence legislation, nor undertake any of the acts prohibited by the FCPA, as summarized above. Neither Isis nor any director, officer, employee, agent or consultant of the Company will submit to extortion as a condition of doing business.