

FORM PTO-1595
1-31-92
ISIS-2422

07-13-1998

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office



To The Honorable Commissioner of Patents
thereof.

100761850

the attached original documents or copy

1. Name of conveying party(ies):
Vasulinga Ravikumar, Dennis Mulvey, Douglas L.
Cole and Philip Dan Cook

MRO 3-2-98

Additional name(s) of conveying party(ies)
attached? () YES (X) NO

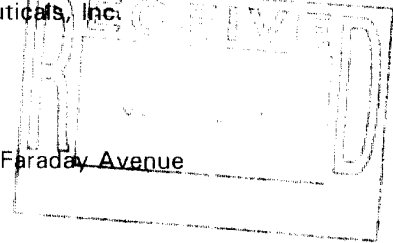
3. Nature of Conveyance:
() Assignment () Merger
() Security Agreement
() Change of Name
(X) Other: **Cross-Reference of Assignment Originally
Recorded in S.N. 08/099,075 filed December 17, 1996
at Reel 8273 Frame 0596**
Execution Date: March 4, 1994 and February 24, 1994

2. Name and address of receiving party(ies):
Name: ISIS Pharmaceuticals, Inc.
Internal Address:

Street Address: 2292 Faraday Avenue

City Carlsbad

State California ZIP 92008
Additional name(s) & address attached? () YES (X) NO



4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
08,789,443

B. Patent No.(s)

Additional numbers attached? () YES (X) NO

5. Name and address of party to whom correspondence
concerning documents should be mailed:
Name: **Joseph Lucci**
Internal Address: WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
Philadelphia, Pennsylvania 19103-7301

Street Address: WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS LLP
One Liberty Place - 46th Floor
1650 Market Street
Philadelphia, Pennsylvania 19103-7301

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41):.....\$40.00
(X) Enclosed
() Authorized to be charged to Deposit Account
Number 23-3050

8. Please charge any deficiency or credit any
overpayment to Deposit Account Number 23-3050

DO NOT USE THIS SPACE

9. Statement and signature.
*To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true
copy of the original document.*

Joseph Lucci/33,307
Name of Person Signing/Reg. No.

Joseph Lucci
Signature

June 29, 1998
Date

Total number of pages including cover sheet, attachments, and document: 16

Mail documents to be recorded with required cover sheet information to:

07/10/1998 DCDATES 00000110 08789443

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Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

PATENT

REEL: 9302 FRAME: 0113

DOCKET NO.: ISIS-1019

(Pending Application;
Serial No. Known)

A S S I G N M E N T

WHEREAS, we Vasulinga Ravikumar, Dennis Mulvey, Douglas L. Cole and Phillip Dan Cook, hereinafter referred to as the assignors, residing respectively at 2325 Via Francesca #J, Carlsbad, CA 92008, 405 Brook Hollow Drive, Conroe, TX 77385, 4992 Smith Canyon Court, San Diego, CA 92130 and 7340 Bolero Street, Carlsbad, CA 92009 are the joint inventors of certain inventions or improvements for which we have made application for Letters Patent to the United States, identified as Serial No. 08/099,075, filed July 29, 1993, entitled **Processes and Intermediates for Phosphorous-Containing Covalent Linkages**; and

WHEREAS, ISIS Pharmaceuticals, Inc., hereinafter referred to as the assignee, of Carlsbad Research Center, a corporation of California, USA is desirous of acquiring the entire right, title and interest in and to the said inventions or improvements and in and to the said application, and in, to and under any and all Letters Patent which may be granted on or as a result thereof in any and all countries:

NOW, THEREFORE, for and in consideration of the sum of One Dollar (\$1.00) to each of us in hand paid by said assignee, and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the said assignors, have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over to said assignee, the entire right, title and interest in and to said inventions or improvements and said application and any and all continuations, divisions and renewals of and substitutes for said application, and in, to and under any and all Letters Patent which may be granted on or as a result thereof in the United States and any and all other countries, and any reissue or reissues or extension or extensions of said Letters Patent, and assign to and authorize said assignee, to file in our names applications for Letters Patent in all countries, the same to be held and enjoyed by said assignee, its successors, assigns, nominees or legal representatives, to the full end of the term or terms for which said Letters Patent respectively may be granted, reissued or extended, as fully and entirely as the same would have been held and enjoyed by us had this assignment, sale and transfer not been made.

AND we hereby covenant that we have full right to convey the entire interest herein assigned, and that we have not executed and will not execute any agreement in conflict herewith, and we further covenant and agree that we will each time request is made and without undue delay, execute and deliver all such papers as may be necessary or desirable to perfect the title to said inventions or improvements, said application and said Letters Patent to said assignee, its successors, assigns, nominees, or legal representatives, and each of us agrees to communicate to said assignee or to its nominee all known facts respecting said

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Joint Inventors

inventions or improvements, said application and said Letters Patent, to testify in any legal proceedings, to sign all lawful papers to execute all disclaimers and divisional, continuing, reissue and foreign applications, to make all rightful oaths, and generally to do everything possible to aid said assignee, its successors, assigns, nominees and legal representatives to obtain and enforce for its or their own benefit proper patent protection for said inventions or improvements in any and all countries.

AND we hereby authorize and request the Commissioner of Patents and Trademarks of the United States and any official of any country or countries foreign to the United States whose duty it is to issue patents on applications as aforesaid, to issue to said assignee, as assignee of the entire right, title and interest, any and all Letters Patent for said inventions or improvements, including any and all Letters Patent of the United States which may be issued and granted on or as a result of the application aforesaid, in accordance with the terms of this assignment.

IN WITNESS WHEREOF, we have hereunto set our hands and seals.

V. Ravikumar (L.S.)
Vasulinga Ravikumar

Dennis M. Mulvey (L.S.)
Dennis Mulvey

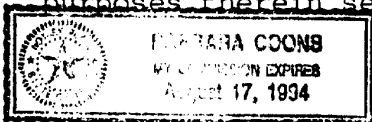
Douglas L. Cole (L.S.)
Douglas L. Cole

Phillip Dan Cook (L.S.)
Phillip Dan Cook

[WHERE ALL INVENTORS SIGN BEFORE THE SAME NOTARY:]

24th
COUNTY OF Montgomery SS

On this 4th day of March, 1934, before me personally came the above named Dennis Mulvey to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.



Barbara Coons
Notary Public

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[WHERE INVENTORS SIGN BEFORE SEPARATE NOTARIES:]

State of California

COUNTY OF San Diego SS

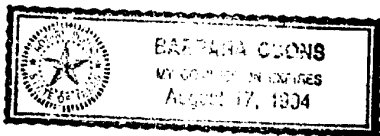
On this 24th day of February, 1994, before me personally came the above named Vasalinga Ravikumar, Douglas L. Cole, Phillip D. Cole to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.



Charmaine G. Webb
Notary Public

Jeffrey
COUNTY OF Montgomery SS

On this 9th day of March, 1994, before me personally came the above named Shannon M. Mules to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.



Barbara Coons
Notary Public

COUNTY OF _____ SS

On this _____ day of _____, 19____, before me personally came the above named _____ to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.

Notary Public

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Joint Inventors

COUNTY OF _____ SS

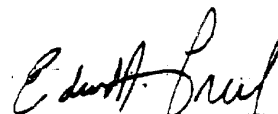
On this _____ day of _____, 19__, before me personally came the above named _____ to me personally known and known to me to be the same individual who executed the foregoing assignment, and who acknowledged to me that execution of the same was of that person's own free will for the use and purposes therein set forth.

Notary Public

State of Delaware
Office of the Secretary of State PAGE 1

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AGREEMENT OF MERGER, WHICH MERGES:
"ISIS PHARMACEUTICALS", A CALIFORNIA CORPORATION,
WITH AND INTO "ISIS PHARMACEUTICALS, INC." UNDER THE NAME OF "ISIS PHARMACEUTICALS, INC.", A CORPORATION ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF DELAWARE, AS RECEIVED AND FILED IN THIS OFFICE THE NINETEENTH DAY OF APRIL, A.D. 1991, AT 12:30 O'CLOCK P.M.





Edward J. Freel, Secretary of State

AUTHENTICATION:

DATE: 7563279

07-05-95

2258177 8100M

950147850

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REEL: 9302 FRAME: 0118

AGREEMENT AND PLAN OF MERGER

This AGREEMENT AND PLAN OF MERGER (the "Merger Agreement") is made as of April 14, 1991, by and between Isis Pharmaceuticals, a California corporation ("Isis California"), and Isis Pharmaceuticals, Inc., a Delaware corporation ("Isis Delaware"). Isis California and Isis Delaware are sometimes referred to as the "Constituent Corporations."

The authorized capital stock of Isis California consists of 20,000,000 shares of Common Stock, without par value, and 15,000,000 shares of Preferred Stock, without par value, of which 6,250,000 shares have been designated as "Series A Preferred Stock," 530,000 shares have been designated as "Series B Preferred Stock" and 5,000,000 shares have been designated as "Series C Preferred Stock." The authorized capital stock of Isis Delaware consists of 50,000,000 shares of Common Stock, \$.001 par value, and 15,000,000 shares of Preferred Stock, \$.001 par value, of which 6,250,000 shares have been designated as "Series A Preferred Stock," 530,000 shares have been designated as "Series B Preferred Stock" and 5,000,000 shares have been designated as "Series C Preferred Stock."

The directors of the Constituent Corporations deem it advisable and to the advantage of said corporations that Isis California merge into Isis Delaware upon the terms and conditions herein provided.

NOW, THEREFORE, the parties do hereby adopt the plan of reorganization encompassed by this Merger Agreement and do hereby agree that Isis California shall merge into Isis Delaware on the following terms, conditions and other provisions:

I. TERMS AND CONDITIONS

1.1 Merger. Isis California shall be merged with and into Isis Delaware (the "Merger"), and Isis Delaware shall be the surviving corporation (the "Surviving Corporation") effective upon the date when this Merger Agreement is filed with the Secretary of State of the State of Delaware (the "Effective Date").

1.2 Succession. On the Effective Date, Isis Delaware shall continue its corporate existence under the laws of the State of Delaware, and the separate existence and corporate organization of Isis California, except insofar as it may be continued by operation of law, shall be terminated and cease.

1.3 Transfer of Assets and Liabilities. On the Effective Date, the rights, privileges, powers and franchises, both of a public as well as of a private nature, of each of the Constituent Corporations shall be vested in and possessed by the Surviving

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Corporation, subject to all of the disabilities, duties and restrictions of or upon each of the Constituent Corporations; and all and singular rights, privileges, powers and franchises of each of the Constituent Corporations, and all property, real, personal and mixed, of each of the Constituent Corporations, and all debts due to each of the Constituent Corporations on whatever account, and all things in action or belonging to each of the Constituent Corporations shall be transferred to and vested in the Surviving Corporation; and all property, rights, privileges, powers and franchises, and all and every other interest, shall be thereafter the property of the Surviving Corporation as they were of the Constituent Corporations, and the title to any real estate vested by deed or otherwise in either of the Constituent Corporations shall not revert or be in any way impaired by reason of the Merger; provided, however, that the liabilities of the Constituent Corporations and of their shareholders, directors and officers shall not be affected and all rights of creditors and all liens upon any property of either of the Constituent Corporations shall be preserved unimpaired, and any claim existing or action or proceeding pending by or against either of the Constituent Corporations may be prosecuted to judgment as if the Merger had not taken place except as they may be modified with the consent of such creditors and all debts, liabilities and duties of or upon each of the Constituent Corporations shall attach to the Surviving Corporation, and may be enforced against it to the same extent as if such debts, liabilities and duties had been incurred or contracted by it.

1.4 Common Stock of Isis California and Isis Delaware. On the Effective Date, by virtue of the Merger and without any further action on the part of the Constituent Corporations or their shareholders, (i) each share of Common Stock of Isis California issued and outstanding immediately prior thereto (as adjusted for the .7-for-1 reverse stock split by Isis California in March 1991) shall be changed and converted into one fully paid and nonassessable share of the Common Stock of Isis Delaware; and (ii) each share of Common Stock of Isis Delaware issued and outstanding immediately prior thereto shall be cancelled and returned to the status of authorized but unissued shares.

1.5 Preferred Stock of Isis California and Isis Delaware. On the Effective Date, by virtue of the Merger and without any further action on the part of the Constituent Corporations or their shareholders, (i) each share of Series A Preferred Stock of Isis California issued and outstanding immediately prior thereto shall be changed and converted into one fully paid and nonassessable share of Series A Preferred Stock of Isis Delaware, (ii) each share of Series B Preferred Stock of Isis California issued and outstanding immediately prior thereto shall be changed and converted into one fully paid and nonassessable share of Series B Preferred Stock of Isis Delaware, and (iii) each share of Series C Preferred Stock of Isis California issued and outstanding

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immediately prior thereto shall be changed and converted into one fully paid and nonassessable share of Series C Preferred Stock of Isis Delaware.

1.6 Stock Certificates. On and after the Effective Date, all of the outstanding certificates which prior to that time represented shares of the Common Stock or of the Preferred Stock of Isis California shall be deemed for all purposes to evidence ownership of and to represent the shares of Isis Delaware into which the shares of Isis California represented by such certificates have been converted as herein provided and shall be so registered on the books and records of the Surviving Corporation or its transfer agents. The registered owner of any such outstanding stock certificate shall, until such certificate shall have been surrendered for transfer or conversion or otherwise accounted for to the Surviving Corporation or its transfer agent, have and be entitled to exercise any voting and other rights with respect to and to receive any dividend and other distributions upon the shares of Isis Delaware evidenced by such outstanding certificate as above provided.

1.7 Options. On the Effective Date, the Surviving Corporation will assume and continue all of Isis California's stock option plans in existence on the Effective Date, including without limitation the 1989 Stock Option Plan, and the outstanding and unexercised portions of all options to purchase Common Stock of Isis California (as adjusted for the .7-for-1 reverse stock split by Isis California in March 1991), including without limitation all options outstanding under such stock option plan and any other outstanding options, shall become options to purchase the same number of shares of Common Stock of Isis Delaware, with no other changes in the terms and conditions of such options. Effective on the Effective Date, Isis Delaware hereby assumes the outstanding and unexercised portions of such options and the obligations of Isis California with respect thereto.

1.8 Warrants. On the Effective Date, the Surviving Corporation will assume and continue all of Isis California's warrants, and the outstanding and unexercised portions of all warrants to purchase Common Stock of Isis California (as adjusted for the .7-for-1 reverse stock split by Isis California in March 1991) shall become warrants to purchase the same number of shares of Common Stock of Isis Delaware, and the outstanding and unexercised portions of all warrants to purchase Series B Preferred Stock of Isis California shall become warrants to purchase the same number of shares of Series B Preferred Stock of Isis Delaware, with no other changes in the terms and conditions of such warrants including exercise prices. Effective on the Effective Date, Isis Delaware hereby assumes the outstanding and unexercised portions of all such warrants and the obligations of Isis California with respect thereto.

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1.9 Employee Benefit Plans. On the Effective Date, the Surviving Corporation shall assume all obligations of Isis California under any and all employee benefit plans in effect as of such date with respect to which employee rights or accrued benefits are outstanding as of such date; provided, however, that one share of Common Stock of Isis Delaware shall be substituted for each share of Common Stock of Isis California (if any) thereunder (as adjusted for the .7-for-1 reverse stock split by Isis California in March 1991). On the Effective Date, the Surviving Corporation shall adopt and continue in effect all such employee benefit plans upon the same terms and conditions as were in effect immediately prior to the Merger and shall reserve that number of shares of Isis Delaware Common Stock with respect to each such employee benefit plan as is equal to the number of shares of Isis California Common Stock (if any) so reserved on the Effective Date (as adjusted for the .7-for-1 reverse stock split by Isis California in March 1991).

II. CHARTER DOCUMENTS, DIRECTORS AND OFFICERS

2.1 Certificate of Incorporation and Bylaws. The Certificate of Incorporation and Bylaws of Isis Delaware in effect on the Effective Date shall continue to be the Certificate of Incorporation and Bylaws of the Surviving Corporation.

2.2 Directors. The directors of Isis Delaware immediately preceding the Effective Date shall become the directors of the Surviving Corporation on and after the Effective Date to serve until the expiration of their terms and until their successors are elected and qualified.

2.3 Officers. The officers of Isis Delaware immediately preceding the Effective Date shall become the officers of the Surviving Corporation on and after the Effective Date to serve at the pleasure of its Board of Directors.

III. MISCELLANEOUS

3.1 Further Assurances. From time to time, and when required by the Surviving Corporation or by its successors and assigns, there shall be executed and delivered on behalf of Isis California such deeds and other instruments, and there shall be taken or caused to be taken by it such further and other action, as shall be appropriate or necessary in order to vest or perfect in or to conform of record or otherwise, in the Surviving Corporation the title to and possession of all the property, interests, assets, rights, privileges, immunities, powers, franchises and authority of Isis California and otherwise to carry out the purposes of this Merger Agreement, and the officers and directors of the Surviving Corporation are fully authorized in the name and on

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behalf of Isis California or otherwise to take any and all such action and to execute and deliver any and all such deeds and other instruments.

3.2 Amendment. At any time before or after approval by the shareholders of Isis California, this Merger Agreement may be amended in any manner (except that, after the approval of the Merger Agreement by the shareholders of Isis California, the principal terms may not be amended without the further approval of the shareholders of Isis California) as may be determined in the judgment of the respective Board of Directors of Isis Delaware and Isis California to be necessary, desirable, or expedient in order to clarify the intention of the parties hereto or to effect or facilitate the purpose and intent of this Merger Agreement.

3.3 Conditions to Merger. The obligation of the Constituent Corporations to effect the transactions contemplated hereby is subject to satisfaction of the following conditions (any or all of which may be waived by either of the Constituent Corporations in its sole discretion to the extent permitted by law):

(a) the Merger shall have been approved by the shareholders of Isis California in accordance with applicable provisions of the General Corporation Law of the State of California; and

(b) Isis California, as sole stockholder of Isis Delaware, shall have approved the Merger in accordance with the General Corporation Law of the State of Delaware; and

(c) any and all consents, permits, authorizations, approvals, and orders deemed in the sole discretion of Isis California to be material to consummation of the Merger shall have been obtained.

3.4 Abandonment or Deferral. At any time before the Effective Date, this Merger Agreement may be terminated and the Merger may be abandoned by the Board of Directors of either Isis California or Isis Delaware or both, notwithstanding the approval of this Merger Agreement by the shareholders of Isis California or Isis Delaware, or the consummation of the Merger may be deferred for a reasonable period of time if, in the opinion of the Boards of Directors of Isis California and Isis Delaware, such action would be in the best interest of such corporations. In the event of termination of this Merger Agreement, this Merger Agreement shall become void and of no effect and there shall be no liability on the part of either Constituent Corporation or its Board of Directors or shareholders with respect thereto, except that Isis California shall pay all expenses incurred in connection with the Merger or in respect of this Merger Agreement or relating thereto.

3.5 Counterparts. In order to facilitate the filing and recording of this Merger Agreement, the same may be executed in

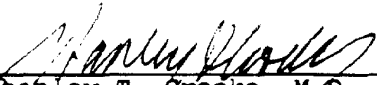
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any number of counterparts, each of which shall be deemed to be an original.

IN WITNESS WHEREOF, this Merger Agreement, having first been duly approved by the Board of Directors of Isis California and Isis Delaware, is hereby executed on behalf of each said corporation and attested by their respective officers thereunto duly authorized.


ISIS PHARMACEUTICALS,
a California corporation

By 
Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board, President
and Chief Executive Officer


ATTEST:


Alan C. Mendelson
Secretary

ISIS PHARMACEUTICALS, INC.,
a Delaware corporation

By 
Stanley T. Crooke, M.D., Ph.D.
Chairman of the Board, President
and Chief Executive Officer

ATTEST:


Alan C. Mendelson
Secretary

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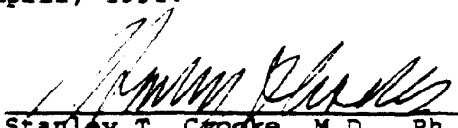
ISIS PHARMACEUTICALS

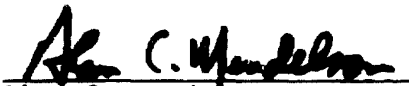
OFFICERS' CERTIFICATE OF APPROVAL OF MERGER

The undersigned, Stanley T. Crooke and Alan C. Mendelson, do hereby certify that:

1. They are the President and Secretary, respectively, of Isis Pharmaceuticals, a California corporation (the "Corporation").
2. The Agreement and Plan of Merger attached to this Certificate providing for the merger of the Corporation with and into Isis Pharmaceuticals, Inc., a Delaware corporation, was duly approved by the Board of Directors and by the shareholders of the Corporation.
3. The Corporation has two authorized classes of shares, designated Common Stock and Preferred Stock. The number of shares of Common Stock outstanding and entitled to vote upon the merger was two million thirty-two thousand eight hundred (2,032,800) shares. The number of shares of Preferred Stock outstanding and entitled to vote upon the merger was eight million four hundred ninety-three thousand nine hundred eighty-one (8,493,981) shares.
4. The terms of the Agreement and Plan of Merger were approved by the Corporation by the vote of the number of shares of Common Stock and Preferred Stock of the Corporation which equaled or exceeded the vote required. The percentage vote required for the Common Stock for such approval was more than fifty percent (50%). The percentage vote required for the Preferred Stock for such approval was more than fifty percent (50%).

IN WITNESS WHEREOF, the undersigned have executed this Certificate this 19th day of April, 1991.


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


Alan C. Mendelson
Secretary

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Each of the undersigned declares under penalty of perjury that he has read the foregoing Certificate and knows the contents thereof and that the same is true of his own knowledge.

Executed at Carlsbad, California on April 19, 1991.


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


Alan C. Mendelson
Secretary

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2.


ISIS PHARMACEUTICALS, INC.

OFFICERS' CERTIFICATE OF APPROVAL OF MERGER

The undersigned, Stanley T. Crooke and Alan C. Mendelson, do hereby certify that:

1. They are the President and Secretary, respectively, of Isis Pharmaceuticals, Inc., a Delaware corporation (the "Corporation").
2. The Agreement and Plan of Merger attached to this Certificate providing for the merger of Isis Pharmaceuticals, a California corporation, with and into the Corporation was duly approved by the Board of Directors and by the stockholders of the Corporation.
3. The Corporation has two authorized classes of shares, designated Common Stock and Preferred Stock. The number of shares of Common Stock outstanding and entitled to vote upon the merger was One Thousand (1,000) shares of Common Stock. There are no shares of Preferred Stock outstanding.
4. The terms of the Agreement and Plan of Merger were approved by the Corporation by the vote of the number of shares of Common Stock of the Corporation which equaled or exceeded the vote required. The percentage vote required for such approval was more than fifty percent (50%).

IN WITNESS WHEREOF, the undersigned have executed this Certificate this 14th day of April, 1991.


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

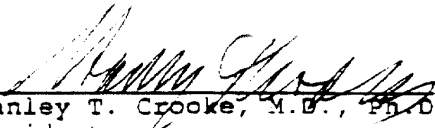

Alan C. Mendelson
Secretary

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1.

Each of the undersigned declares under penalty of perjury that he has read the foregoing Certificate and knows the contents thereof and that the same is true of his own knowledge.

Executed at Carlsbad, California on April 19, 1991.


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


Alan C. Mendelson
Secretary

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