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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,550	04/30/2007	5977089		8068

25000 7590 01/16/2008

GILEAD SCIENCES INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 01/16/2008

Please find below and/or attached an Office communication concerning this application or proceeding.

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(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Daniel B. Ravicher, Esq.
Public Patent Foundation, INC.
1375 Broadway, Suite 600
New York, NY 10018

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/008,550*.

PATENT NO. *5977089*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/008,550	Patent Under Reexamination 5977089	
	Examiner Dwayne C. Jones	Art Unit 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a☒ Responsive to the communication(s) filed on *30 April 2007* . b☐ This action is made FINAL.
c☒ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire _____ month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-3* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1-3* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____ .
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

DETAILED ACTION

Ex Parte Reexamination
by
Third Party Requester:

First Action on the Merits

Procedural Posture

On 03/23/2007:	A Request for *Ex Parte* Reexamination by a Third Party Requester was filed.
On 04/03/2007:	A Notice of Failure to Comply with *Ex Parte* Reexamination Request Filing Requirements (37 CFR 1.510(c)) was mailed.
On 04/30/2007:	A Corrected Request for *Ex Parte* Reexamination by a Third Party Requester was filed for U.S. Patent No. 5,977,089 ('089 Patent) now assigned control number 90/008,550.
On 07/13/2007:	A Determination GRANTING the Request for *Ex Parte* Reexamination by a Third Party Requester was mailed.
	A statement under 37 CFR 1.530 has not been received from the Patent Owner.

Priority

1. The '089 Patent issued to Arimilli et al. on 11/02/1999 filed on 11/06/1998 as U.S. Application No. 09/187,763, which is a continuation of U.S. Patent No. 08/900,746 filed on 07/25/1997, which is further based on U.S. Provisional Application No. 60/022,708 filed on 07/26/1996. The Third Party Requester asserts that the three (3) claims of the '089 Patent (patent undergoing reexamination), which are directed to (R)-bis(POC)PMPA (9-[2-[[bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinoyl]propyl]adenine), are not entitled to claim

priority to the provisional application of 60/022,708 because the 60/022,708 specification did not describe the invention in sufficient detail to show one of ordinary skill in the art that the '089 Patent possessed the claimed invention at the time of filing the 60/022,708 application (See pages 4-7 of the Request). Accordingly, the Third Party Requester asserts that the written description requirement was not satisfied until 07/25/1997, which is the filing date of 08/900,746.

These assertions regarding the priority date are not found persuasive for the following reasons. First, 60/022,708 lists a synthetic method to yield the compound of formula (I), which is the generic compound that embraces the claimed bis(POC)PMPA compound and its enantiomers (See pages 2, 3, 8, and 9). Second, Example 7 of 60/022,708 is specifically directed to the synthesis of bis-isopropyl oxymethyl carbonate of PMPA (See pages 23 and 24). Third, Table 1 of 60/022,708 specifically lists the prodrug carbonate compound of bis-isopropylCOM PMPA (See page 34). Fourth, 60/022,708 describes that "[t]he compounds of this invention are optionally enriched or resolved at the carbon atom chiral center linked to R^1 in accordance with prior findings associating optimal antiviral activity with the configuration at this site. Thus, where R^1 is methyl, the center will be in (R) configuration" (See page 6). Fifth, 60/022,708 describes that the compounds and compositions with pharmaceutically acceptable carriers of this invention are useful in the treatment or prophylaxis of one or more viral infections in a variety modes of administration, in particular oral administration (See pages 9-14).

In view of the sundry descriptions and examples provided in 60/022,708, there is adequate written description and support under 35 USC 112, 1st paragraph for

(R)-bis(POC)PMPA as claimed in '089 Patent (patent undergoing reexamination). Accordingly, the Third Party Requester's allegations regarding the lack of written description in 60/022,708 are not found convincing. Therefore, the earliest possible effective filing date for the '089 Patent (patent undergoing reexamination) is 07/26/1996, which is the filing date of provisional 60/022,708.

References Cited by the Third Party Requester

New References Cited:

1. **Bischofberger et al.**,"Bis(POC)PMPA, an Orally Bioavailable Prodrug of the Antiretroviral agent PMPA," *Conference on Retroviruses and Opportunistic Infections*, 4th:104 (abstract no. 214, January 22-26, 1997, (hereinafter referred to as **Bischofberger et al.**).
2. **Holy et al.** of EP 0206459 B1, published on 12/30/1986, (hereinafter referred to as **Holy et al.**).
3. **Notari, R. E,**, "Prodrug Design," *Pharmaceutical Therapy*, 14:25-53, 1981. (hereinafter referred to as **Notari**).

Old Reference Cited:

4. **Jones et al.**, "Minireview: Nucleotide Prodrugs," *Antiviral Research*, 27:1-17, 1995, (hereinafter referred to as **Jones et al.**).

Legal Standards

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

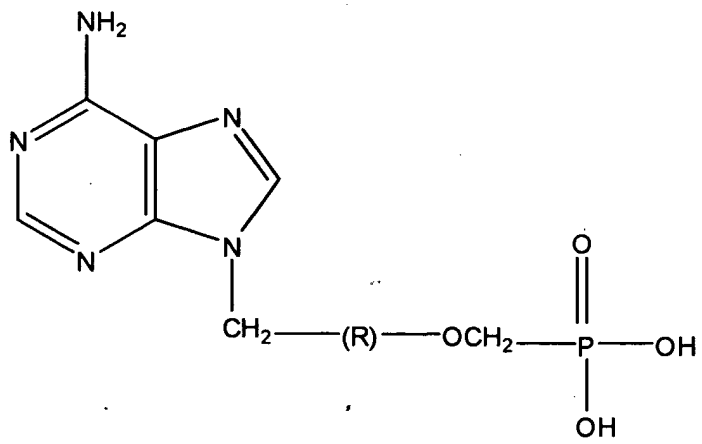
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim Rejections - 35 USC § 103

3. **Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holy et al.** (*EP 0206459 B1, published on 12/30/1986*) **in view of Jones et al.** ("*Minireview: Nucleotide Prodrugs," Antiviral Research, 27:1-17, 1995*) **in further view of Notari** (*Prodrug Design," Pharmaceutical Therapy, 14:25-53, 1981*).

Claim 1. (R)-bis(POC)PMPA.
Claim 2. A composition comprising (R)-bis(POC)PMPA and a pharmaceutically acceptable carrier.
Claim 3. A method comprising orally administering to a patient infected with virus or at risk to viral infection a therapeutically effective amount of (R)-bis(POC)PMPA.

Regarding claims 1-3, Holy et al. teach anti-viral treatments made from 9-(phosphonomethoxyalkyl)adenines of general formula I,



wherein R is a CH_2, $CH(CH_3)$, CH_2CH_2 or $CH(OCH_3)CH_2$ group and the salts thereof with alkali metals, ammonia or amines, and in particular the compound 9-[2-(phosphonylmethoxy)-propyl]adenine (PMPA), which are phosphonomethoxy nucleotides (See page 2, lines 23-38; page 4, lines 27-30; page 5, line 29 of Example 2; page 8, line 20). Holy et al. also teach that the compounds of general formula I can be stored as free acids or salts (See page 4, lines 9-12).

The claimed subject matter differs from the teachings of Holy et al. by requiring the PMPA compounds to be present in a prodrug form with a carbonate moiety. However, Holy et al. teach the use of phosphonomethoxy nucleotides, in particular PMPA, and their salts to treat viruses.

Jones et al. teach that nucleoside and nucleotide analogues have great therapeutic potential for the treatment of viral diseases and cancer (See page 2, 1st paragraph). Jones et al. acknowledge that nucleotides have some disadvantages over nucleosides. For example, Jones et al. teach that nucleotides (which include PMPA) demonstrate low permeability and bioavailability due to the negative charge(s) on the phosphorous entail(s) nucleotide (See page 4, 1st paragraph). Accordingly, Jones et al. teach and provide the skilled artisan with ample motivation to overcome these difficulties with nucleotides by using nucleotide prodrugs. In addition, Jones et al. teach on page 4, 2nd paragraph that the:

> "[m]asking of the negative charges(s) on the phosphorous by suitable functionalities, which can be converted chemically or biologically to the parent nucleotide, can make nucleotides orally bioavailable, increase intracellular delivery, and alter pharmacokinetics/tissue distribution/metabolism resulting in improved efficacy and target organ specificity."

Jones et al. also teach prodrugs of bis(acyloxymethyl) esters of phosphate prodrugs, such as bis(pivaloyloxymethyl)PMEA (See page 5, 1st paragraph). In addition, Jones et al. provide

one having ordinary skill in the art with a reasonable expectation of success in converting antiviral nucleotides (charged compounds) into prodrug (uncharged or neutral) forms for therapeutic use.

The claimed subject matter differs from the teachings of Holy et al. in view of Jones et al. by requiring the PMPA compounds to be present in a prodrug form with a carbonate moiety. However, Holy et al. teach the use of phosphonomethoxy nucleotides, in particular PMPA, and their salts to treat viruses, and Jones et al. specifically teach and provide motivation to the skilled artisan in converting antiviral nucleotides (charged compounds) into prodrug (uncharged or neutral) forms for therapeutic use.

Notari teaches that known drugs with disadvantages such as undesirable stability or solubility could be improved through the creation of a prodrug, in particular enzyme-reversible prodrug linkages that include esters, phosphates, carbonates, and hemiesters, wherein the original drug provides either the carboxylic acid or the hydroxyl group (See page 27, 1st full paragraph). Notari teaches and provides motivation to the skilled artisan that prodrugs increase the bioavailability, solubility, stability, site specificity, and extended duration of pharmaceuticals (See page 26, 1st full paragraph and Table 1).

The determination of preparing and formulating a pharmaceutical (antiviral) agent in a prodrug form having the optimum therapeutic index, while minimizing unwanted and/or adverse side-effects, is well within the level of the skilled artisan. In addition, the skilled artisan would recognize that the most obvious selection of a carbonate moiety for a prodrug would have been achieved with small alkyl or other small, neutral groups provided that these small alkyl (neutral) groups would not introduce enough steric hinderance to interfere with the enzymatic cleavage of

the carbonate prodrug moiety from the antiviral compound. Thus the selection of bis-isopropyl carbonate moiety (small alkyl, neutral group) is rendered an obvious choice to the skilled artisan. At the time of the invention, one of ordinary skill the art would have been motivated to prepare bis-carbonate prodrugs of 9-(phosphonomethoxyalkyl)adenines by combining the antiviral compound of Holy et al. with the carbonate prodrugs as taught by Notari for the purposes as established by Jones et al. and Notari et al. to arrive at the instant invention, with the reasonable expectation of success to make ă carbonate prodrug of 9-(phosphonomethoxyalkyl)adenines that provides an antiviral drug (composition) with increased bioavailability, stability, and solubility of the antiviral drug.

The Bischofberger et al. Reference Is Not Deemed as Valid Prior Art

4. As previously indicated in the Determination Granting the *Ex Parte* Reexamination of the '089 Patent mailed 07/13/2007, no substantial new question of patentability was raised by the Request for Reexamination for the prior art reference of Bischofberger et al. Bischofberger et al. is not available as valid prior art against the claims of U.S. Patent No. 5,977,089 because its date of publication (January 22-26, 1997) is after the effective filing date of U.S. Patent No. 5,977,089 (patent undergoing reexamination) (July 26, 1996). In fact, the **Priority** Section, stated *supra*, of this Office Action provides a detailed discussion of the adequate written description that is contained in 60/022,708. Accordingly, the Bischofberger et al. reference is not deemed as valid prior art, thus a rejection based on Bischofberger et al. alone or in combination with another reference is not warranted because this reference **does not** create a substantial new question of patentability with respect to claims 1-3 of U.S. Patent No. 5,977,089.

Conclusion

5. Claims 1-3 are pending and undergoing *Ex Parte* Reexamination.

6. Claims 1-3 are rejected.

Extensions of Time

Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *Ex Parte* reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extensions of time in *Ex Parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Future Amendment

Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37 CFR 1.20(c).

In particular, 37 CFR 1.530(i) states: "All amendments must be made relative to the patent specification, including the claims, and drawings, which are in effect as of the date of filing the request for reexamination." As a result each amendment to the claims should be made relative to the originally patented claims and not to the previous amendment. Any changes must include brackets (not strikethroughs) for the matter to be omitted and underlining fro added matter (See 37 CFR 1.530(f)(1)(2)). The Patent Owner is directed to MPEP 2250 (IV) containing examples of claim amendments in reexamination proceedings.

Please provide a complete listing of all pending claims and their respective status (i.e., original, cancelled, amended, new) undergoing reexamination that complies with 37 CFR 1.530(d)-(j).

Ongoing Duty to Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 5,977,089 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Service of Papers

After the filing of a request for reexamination by a third party requester, any document filed by either the patent owner or the third party requester must be served on the other party (or parties where two or more third party requester proceedings are merged) in the reexamination proceeding in the manner provided in 37 CFR 1.248 (See 37 CFR 1.550(f)).

NOTICE RE PATENT OWNER'S CORRESPONDENCE ADDRESS

Effective May 16, 2007, 37 CFR 1.33(c) has been revised to provide that:

The patent owner's correspondence address for all communications in an *ex parte* reexamination or an *inter partes* reexamination is designated as the correspondence address of the patent.

> *Revisions and Technical Corrections Affecting Requirements for Ex Parte and Inter Partes Reexamination*, 72 FR 18892 (April 16, 2007)(Final Rule)

The correspondence address for any pending reexamination proceeding not having the same correspondence address as that of the patent is, by way of this revision to 37 CFR 1.33(c), automatically changed to that of the patent file as of the effective date.

This change is effective for any reexamination proceeding which is pending before the Office as of May 16, 2007, including the present reexamination proceeding, and to any reexamination proceeding which is filed after that date.

Parties are to take this change into account when filing papers, and direct communications accordingly.
In the event the patent owner's correspondence address listed in the papers (record) for the present proceeding is different from the correspondence address of the patent, it is strongly encouraged that the patent owner affirmatively file a Notification of Change of Correspondence Address in the reexamination proceeding and/or the patent (depending on which address patent owner desires), to conform the address of the proceeding with that of the patent and to clarify the record as to which address should be used for correspondence.

Telephone Numbers for reexamination inquiries:

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

Future Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays-Thursdays from 8:30 am to 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones, may be reached at (571) 272-1535. The official fax No. for the organization where this application is assigned is (571)-273-9900. For status inquires of a general nature refer to the customer service line at (571) 272-7705.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 1-866-217-9197 (toll free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By Mail to:	Mail Stop *Ex Parte* Reexam Central Reexamination Unit Commissioner for Patents United States Patent & Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450
By FAX to:	571-273-9900 Central Reexamination Unit
By hand to:	Customer Service Window Randolph Building 401 Dulany Street Alexandria, VA 22314

December 20, 2007

DWAYNE C. JONES
PRIMARY EXAMINER
CRU - AU 3991

Dwayne C. Jones
Primary Examiner
Art Unit 3991

Conferee:

SPE | 3991

GARY L. KUNZ
PRIMARY EXAMINER
CRU - AU 3991