

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT NO.: 5,977,089
ISSUED: Nov. 2, 1999
TO: Arimilli et al.
FOR: ANTIVIRAL PHOSPHONOMETHOXY
NUCLEOTIDE ANALOGS HAVING
INCREASED ORAL BIOAVAILABILITY

ATTACHMENT TO FORM PTO-1465,
REQUEST FOR *EX PARTE* REEXAMINATION

SIR:

The Public Patent Foundation (“PUBPAT”), a not-for-profit public service organization that works to protect the public from the harms caused by undeserved patents and unsound patent policy, respectfully requests *ex parte* reexamination under 35 U.S.C. §§ 302 – 307 and 37 C.F.R. § 1.510 of every claim of United States Patent No. 5,977,089 issued November 2, 1999, to Arimilli et al. and assigned to Gilead Sciences, Inc. (“the '089 patent”) because they are all invalid under 35 U.S.C. §§ 102 and 103 and their existence is causing

significant public harm.¹

THE '089 PATENT IS CAUSING SIGNIFICANT PUBLIC HARM

HIV/AIDS is one of the greatest threats to public health faced by the World today. As of November 2006, roughly 40 million people worldwide were living with HIV/AIDS, including more than 1.2 million Americans.² Every person afflicted with HIV/AIDS has the right to obtain the best medical treatment available, without any improper obstacles placed in their way. More specifically, American men, women and children suffering from HIV/AIDS are entitled to access the best pharmaceutical treatments available without undeserved patents making those treatments either too expensive or too limited in supply.

Tenofovir disoproxil fumarate (also referred to as “TDF”, “bis(POC)PMPA fumarate”) is a nucleotide analog reverse transcriptase inhibitor (“NtRTI”) that is a significant treatment for HIV/AIDS patients. The '089 patent claims (R)-bis(POC)PMPA, compositions comprising (R)-bis(POC)PMPA and a pharmaceutically acceptable carrier, and 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.

Gilead is using the '089 patent – and three other patents for which requests for reexamination are being filed concurrently herewith – to prevent anyone else from offering TDF to

1 A copy of the '089 patent is attached hereto as Appendix A.

2 *HIV/AIDS Policy Fact Sheets*, The Henry J. Kaiser Family Foundation, November 2006, available from <http://www.kff.org/hiv/aids/index.cfm>.

HIV/AIDS patients in the United States.³ Not only is the '089 patent being used to deny American HIV/AIDS patients fair access to the medical treatment that they need and deserve, it is also a barrier to further research on TDF here in the United States because there is no exception to patent infringement for such research. In these ways, the '089 patent is unquestionably causing significant public harm to the American people.

Although these issues are not grounds to grant this request for reexamination, PUBPAT respectfully requests that they be considered when determining whether the validity of the '089 patent merits review by your office.

THE SUBSTANTIAL NEW QUESTIONS OF PATENTABILITY

The substantial new questions of patentability raised by this request are the following:

1. Whether claims 1 – 3 of the '089 patent were anticipated or rendered obvious by 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) (“Bischofberger”); and
2. Whether claims 1 – 3 of the '089 patent were rendered obvious by EP 0206459 to Holy et al., published on December 30, 1986 (“Holy”), in light of Notari, “Prodrug Design,” *Pharmaceutical Therapy*, 14:25-53 (1981) (“Notari”), and Jones et al., “Minireview:

³ Approved Drug Products with Therapeutic Equivalence Evaluations, Food and Drug Administration (“Orange Book”).

Nucleotide Prodrugs,” *Antiviral Research*, 27:1-17 (1995) (“Jones”).

These are new questions because neither Bischofberger, Holy nor Notari were of record and Jones was not addressed during prosecution of the '089 patent application. A detailed explanation of the pertinency and manner of applying the cited patents and publications to the claims of the '089 patent is set forth below.⁴

BISCHOFBERGER ANTICIPATED OR RENDERED OBVIOUS THE '089 PATENT

The '089 patent application was filed November 6, 1998. It claims priority as continuation to U.S. patent application no. 08/900,746, which claims priority as a continuation-in-part to a provisional application – No. 60/022,708 – filed July 26, 1996 (“the '708 application”). However, the 3 claims of the '089 patent are not entitled to claim priority to the '708 application's July 26, 1996, filing date, because the '708 application's specification was not sufficient to satisfy the written description requirement of 35 U.S.C. § 112 with respect to the 3 claims of the '089 patent.

In its most recent decision on the matter, the United States Supreme Court held that written description is indeed a separate § 112 statutory requirement above and beyond the best mode and enablement requirements.⁵ Further, the Court of Appeals for the Federal Circuit has also

⁴ Appendix B contains a copy of the cited patents and publications.

⁵ *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736 (2002) (“[A] number of statutory requirements must be satisfied before a patent can issue. The claimed subject matter must be useful, novel, and not obvious. 35 U.S.C. §§ 101-103 (1994 ed. and Supp. V). In addition, the patent application must describe, enable, and set forth the best mode of carrying out the invention. § 112 (1994 ed.). These latter requirements must be satisfied before issuance of the patent, for exclusive patent rights are given in exchange for disclosing the invention to the public.”).

recently reaffirmed that “our precedent clearly recognizes a separate written description requirement.”⁶ To satisfy the separate written description requirement, a specification must describe the claimed invention so that one of ordinary skill in the art can recognize what is claimed. Further, sufficient detail must be included in the specification to show one of ordinary skill in the art that the applicant possessed the claimed invention at the time of the filing of the application.

In this case, the '089 patent contains 3 claims, which are:

1. (R)-bis(POC)PMPA.
2. A composition comprising (R)-bis(POC)PMPA and a pharmaceutically acceptable carrier.
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.

The '708 application did not satisfy the written description requirement with respect to the '089 patent's 3 claims because they all rely on (R)-bis(POC)PMPA, which was not disclosed in the specification of the '708 application. Another example of the significant differences between the specification of the '089 patent and the specification of the '708 application to which it attempts to claim priority are the countless formulas and specific embodiments contained in the '089 patent between 6:55 and 32:17 that are completely absent from the '708 application's specification. That is roughly 26 columns of specification detail that was not in the '708 application's specification.

⁶ *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 922 (Fed. Cir. 2004).

These significant differences in the amount of information disclosed in the specifications of the '708 application and the '089 patent are illustrated in Table 1 below.

<i>Differences</i>	<i>'089 Patent</i>	<i>'708 Application</i>
(R)-bis(POC)PMPA	44:6-47.	Does not exist.
Specific Examples	Numerous formulas and specific compound embodiments. 6:55 – 32:17.	Does not exist.

TABLE 1: Differences Between Specifications of '089 Patent and '708 Application

Since both of these topics are critical to the claims of the '089 patent, the substantial difference in disclosure about them between the specifications of the '708 application and the '089 patent means that the '708 application specification did not describe the invention in sufficient detail to show one of ordinary skill in the art that the '089 patent applicant possessed the claimed invention at the time of the filing of the '708 application. Rather, the applicant can not be said to have satisfied the written description requirement until at least July 25, 1997, the date of the filing of the application to which the '089 patent claims priority as a continuation.

As such, since Bischofberger was published January 22, 1997, it is prior art to the 3 claims of the '089 patent under 35 U.S.C. § 102(a). The chart below sets forth an element-by-element comparison of all 3 claims of the '089 patent to the teaching of Bischofberger. In essence, Bischofberger expressly taught PMPA and bis(POC)PMPA, which is the focus of the '089 patent's disclosure and each of its 3 claims. Bischofberger further taught that “oral administration of bis(POC)PMPA resulted in significantly delayed tumor appearance.” Bischofberger concluded that

“bis(POC)PMPA is a promising agent for the treatment and prophylaxis of HIV infections.” In essence, every element of each the '089 patent's 3 claims was either specifically disclosed by Bischofberger or inherent in its teachings. Therefore, each claim of the '089 patent is invalid and should be canceled.

'089 Patent	Bischofberger
1. (R)-bis(POC)PMPA.	Bischofberger expressly taught bis(POC)PMPA. Inherent in Bischofberger's teaching is the R configuration of a bis(POC)PMPA enantiomer. Even if not inherent, creating an enantiomer of a known drug would have been obvious to one of ordinary skill in the art.
2. A composition comprising (R)-bis(POC)PMPA and a pharmaceutically acceptable carrier.	As discussed above with respect to claim 1, Bischofberger either anticipated or rendered obvious (R)-bis(POC)PMPA. Bischofberger also expressly taught administering bis(POC)PMPA orally to an animal. Inherent in such teaching is that the composition would comprise a pharmaceutically acceptable carrier in addition to the bis(POC)PMPA. Further, it would have been obvious to combine the drug with a pharmaceutically acceptable carrier for use in administering the agent to an animal.
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.	As discussed above with respect to claim 1, Bischofberger either anticipated or rendered obvious (R)-bis(POC)PMPA. Bischofberger also expressly taught administering a therapeutically effective amount of bis(POC)PMPA orally to an animal as an antiviral agent.

**HOLY, IN LIGHT OF NOTARI AND JONES,
RENDERED THE '089 PATENT OBVIOUS**

In addition to being anticipated or rendered obvious by Bischofberger, the '089 patent was also obvious in light of other prior art teachings that phosphonmethoxy nucleotide analogs, including PMPA, were strong treatments for HIV and that carbonate and carbamate could be used to produce prodrugs to increase bioavailability.

Phosphonmethoxy Nucleotide Analogs, Including PMPA, Were Well Known Treatments for HIV

The '089 patent concedes that “the parental compounds have the structure $\text{AOCH}_2\text{P}(\text{O})(\text{OH})_2$ [and they were] well known and have demonstrated antiviral activity.” '089 patent, 4:4-8. Several references confirm this concession regarding the advanced state of the art relating to phosphonmethoxy nucleotide analogs as treatments for HIV/AIDS before the filing of the '089 patent application.

First, EP 0206459 to Holy et al. published on December 30, 1986 (“Holy”) and therefore is prior art to the '089 patent under 35 U.S.C. § 102(b). Holy taught anti-viral treatments made from 9-(Phosphonylmethoxyalkyl) adenines. 2:23-38, 5:29 (Example 2) and 8:20. Further, as discussed above, Bischofberger taught bis(POC)PMPA and that “oral administration of bis(POC)PMPA resulted in significantly delayed tumor appearance.” Bischofberger concluded that “bis(POC)PMPA is a promising agent for the treatment and prophylaxis of HIV infections.”

Since phosphonmethoxy nucleotide analogs, and PMPA specifically, were already well known, the '089 patent application directed itself to the purported invention of (R)-

bis(POC)PMPA, a mere prodrug of PMPA formed using carbonate ester linkage.

Using Carbonate Esters to Produce Prodrugs to Increase Bioavailability Was Known

Putting aside the novelty argument based on Bischofberger made above, if one assumes *arguendo* that the claimed compounds were novel, they were nonetheless obvious in light of prior art references that taught successful adoption of esters in oral drug discovery programs for nucleotide analogs. To be sure, the state of the art relating to prodrugs was quite advanced before the '089 patent application was filed.

For example, Notari, “Prodrug Design,” *Pharmaceutical Therapy*, 14:25-53 (1981) (“Notari”), is prior art to the '089 patent under 35 U.S.C. § 102(b). Notari taught that known drugs with disadvantages such as undesirable stability or solubility could be improved through the creation of a prodrug and that “possible enzyme-reversible prodrug linkages [include] ... carbonate esters.” 27. Notari further taught that:

Although the list [of possible enzyme-reversible prodrug linkages] is short the list of prodrug linkages commonly employed is much shorter. By far the most widely used prodrug linkage is that of an ester wherein the original drug provides either the carboxylic acid or the hydroxyl group. Add to this the phosphates, carbonates and hemiesters and one has accounted for the large majority of prodrugs.

27 (emphasis added). As such, not only were carbonate esters already well known to be useful prodrug linkages, it was also known that the list of esters commonly employed as prodrug linkages was very short.

Further, Jones et al., “Minireview: Nucleotide Prodrugs,” *Antiviral Research*, 27:1-

17 (1995) (“Jones”), is prior art to the '089 patent under 35 U.S.C. § 102(b). Jones taught that ester prodrugs could improve the oral bioavailability of antiviral nucleoside and nucleotide analogs. 2.

Specifically, Jones taught:

Nucleoside and nucleotide analogues have great therapeutic potential for the treatment of viral diseases and cancer. [] The area of nucleotide analogues has received a lot of attention recently due to the discovery of nucleotides with potent antiviral activities (Holy, 1993). Since the negative charge(s) on the phosphorous entail(s) nucleotides with short comings (low permeability and bioavailability), increasing work in the literature is focusing on overcoming these difficulties with nucleotide prodrugs[.]

2. Thus, before the filing of the application leading to the '089 patent, those of ordinary skill in the art were already motivated to develop prodrugs of nucleotide analogs. Jones further disclosed the successful creation of an ester prodrug from PMEA, which is structurally similar to PMPA. 5.

Thus, one of ordinary skill in the art would have been motivated by Notari to produce prodrugs for Holy's antiviral nucleotide analogs because they were taught by Jones to have limited bioavailability and because Jones specifically cited Holy. Jones, 2. One of ordinary skill in the art would have also expected to be able to successfully create such prodrugs by using an ester linkage with carbonate as per the teachings of Notari and Jones. As such, the purported advance of the '089 patent, even if novel, would have been obvious in light of Holy, with Notari and Jones.

Claims 2 and 3 of the '089 patent are simply directed to (a) a composition comprising the PMPA prodrug and a pharmaceutically acceptable carrier and (b) a method of orally administering to a patient infected with a virus the PMPA prodrug. These were well known

applications of beneficial prodrugs and, thus, they too were obvious in light of Holy with Notari and Jones.

The chart below sets forth an element-by-element comparison of each of the 3 claims of the '089 patent to the teachings of Holy, in light of Notari and Jones. In essence, Holy's teaching of antiviral nucleotide analogs, in light of Notari's teaching of prodrugs creation and Jones' teaching that ester prodrugs could improve the oral bioavailability of antiviral nucleotide analogs, rendered each of the '089 patent's claims obvious. As such, each claim of the '089 patent is invalid and should be canceled.

<i>'089 Patent</i>	<i>Holy, with Notari and Jones</i>
1. (R)-bis(POC)PMPA.	Holy taught anti-viral treatments made from PMPA, a nucleotide analog. 2:23-38, 5:29 (Example 2) and 8:20. Jones taught that antiviral nucleotide analogs had limited bioavailability, which Notari taught could be improved through the creation of prodrugs. Jones, 2; Notari, 27. Notari further taught that “possible enzyme-reversible prodrug linkages [include] ... carbonate esters [and] carbamates.” Notari, 27. This is the process that was used by the '089 patent to produce (R)-bis(POC)PMPA. As such, it was obvious in light of the prior art teachings.

<p>2. A composition comprising (R)-bis(POC)PMPA and a pharmaceutically acceptable carrier.</p>	<p>As discussed above with respect to claim 1, Holy, in light of Notari and Jones, rendered (R)-bis(POC)PMPA obvious. Jones and Notari further taught that such prodrugs were administered orally. Jones, 4; Notari, 26. Inherent in such teaching is that the composition would comprise a pharmaceutically acceptable carrier in addition to the drug. Further, it would have been obvious to combine the drug with a pharmaceutically acceptable carrier.</p>
<p>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.</p>	<p>As discussed above with respect to claim 1, Holy, in light of Notari and Jones, rendered (R)-bis(POC)PMPA obvious. Holy and Jones further taught that such drugs were antiviral and Jones and Notari further taught that such prodrugs were administered orally. Jones, 4; Notari, 26. It is inherent in these teachings that a therapeutically effective amount of the drug was administered.</p>

For these reasons, Holy, in light of Notari and Jones, rendered every claim of the '089 patent obvious. As such, each claim of the '089 patent is invalid and should be canceled.

CONCLUSION

For the reasons set forth above, each of the claims of the '089 patent are invalid. As such, PUBPAT respectfully requests that they be reexamined *ex parte* and ultimately canceled.

April 30, 2007

Date

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CERTIFICATE OF SERVICE

The undersigned certifies that a copy of this Request for *Ex Parte* Reexamination in its entirety, including all accompanying documents, is being deposited with the U.S. Postal Service as First Class Mail on the date of the signature below in an envelope addressed to the attorney of record for the assignee of U.S. Patent No. 5,977,089 as provided for in 37 C.F.R. § 1.33(c):

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