IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT NO.: 6,043,230

ISSUED: Mar. 28, 2000

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. 6,043,230 issued March 28, 2000, to Arimilli et al. and assigned to Gilead Sciences, Inc. ("the '230 patent") because they are all invalid under 35 U.S.C. §§ 102 and 103 and their existence is causing significant public harm.[1]

1 A copy of the '230 patent is attached hereto as Appendix A.

THE '230 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 '230 patent claims a method of contacting a cell with an antiviral phosphonomethoxy nucleotide analog prodrug.

Gilead is using the '230 patent – and three other patents for which requests for reexamination are being filed concurrently herewith – to prevent anyone else from offering TDF to HIV/AIDS patients in the United States.[3] Not only is the '230 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

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

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

infringement for such research. In these ways, the '230 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 '230 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 claim 1 of the '230 patent was 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 claim 1 of the '230 patent was 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: 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 '230 patent application. A detailed explanation of the pertinency and manner of applying the cited patents and publications to the claims of the '230

patent is set forth below.[4]

BISCHOFBERGER ANTICIPATED OR RENDERED OBVIOUS THE '230 PATENT

The '230 patent application was filed May 19, 1999. 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 claim of the '230 patent is 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 '230 patent claim.

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 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

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

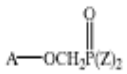
5 *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 736 (2002) ("[A] number of statutory requirements must be satisfied before a patent can issue. The claimed subject matter must be useful, novel, and not obvious. 35 U.S.C. §§ 101-103 (1994 ed. and Supp. V). In addition, the patent 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.").

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

application.

In this case, the '230 patent contains 1 claim, which is:

1. A method comprising contacting a cell with a compound having formula (1a)



(1a)

wherein Z is independently --$OC(R^2)_2OC(O)X(R)_a$, an ester, an amidate or
--H, but at least one Z is --$OC(R^2)_2OC(O)X(R)_a$;
A is the residue of an antiviral phosphonomethoxy nucleotide analog;
X is N or O;
R^2 independently is --H, C_1-C_{12} alkyl, C_5-C_{12} aryl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro or --OR^3 in which R^3 is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl or C_5-C_{12} aryl;
R is independently --H, C_1 -C_{12} alkyl, C_5-C_{12} aryl, C_2 -C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkyenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro, --$N(R^4)_2$ or --OR^3, where R^4 independently is
--H or C_2-C_8 alkyl, provided that at least one R is not H; and
a is 1 when X is O, or 1 or 2 when X is N;
with the proviso that when a is 2 and X is N, (a) two N-linked R groups can be taken together to form a carbocycle or oxygen-containing heterocycle, (b) one N-linked R additionally can be --OR^3 or (c) both N-linked R groups can be --H.

The '708 application did not satisfy the written description requirement with respect to the '230 patent's claim because it relies on a “compound having formula 1(a),” which is not the same as the

"formula 1(a)" that was disclosed in the specification of the '708 application. Another example of the significant differences between the specification of the '230 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 '230 patent between 6:55 and 32:45 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. These significant differences in the amount of information disclosed in the specifications of the '708 application and the '230 patent are illustrated in Table 1 below.

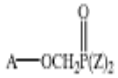
Differences	***'230 Patent***	***'708 Application***
Formula 1(a)	 (1a) 60:20-25.	$A(Z)_n$ (1a) 36:5.
Specific Examples	Numerous formulas and specific compound embodiments. 6:55 – 32:45.	Does not exist.

TABLE 1: Differences Between Specifications of '230 Patent and '708 Application

Since both of these topics are critical to the claim of the '230 patent, the substantial difference in disclosure about them between the specifications of the '708 application and the '230 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 '230 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 '230 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 '230 patent under 35 U.S.C. § 102(a). The chart below sets forth an element-by-element comparison of the claim of the '230 patent to the teaching of Bischofberger. In essence, Bischofberger taught PMPA and bis(POC)PMPA, which is the focus of the '230 patent's disclosure and claim. '230 patent, 44:6–67 (directed to the production of "Bis(POC)PMPA fumarate"). 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." Although Bischofberger may not have specifically disclosed each particular element of the '230 patent's claim, each of those elements are nonetheless either inherent in or rendered obvious by Bischofberger's teachings. Therefore, the claim of the '230 patent is invalid and should be canceled.

'230 Patent	***Bischofberger***
1. A method of contacting a cell with a compound having formula (1a)  (1a) wherein Z is independently --$OC(R^2)_2OC(O)X(R)_a$, an ester, an amidate or -- H, but at least one Z is --$OC(R^2)_2OC(O)X(R)_a$; A is the residue of an antiviral phosphonomethoxy nucleotide analog;	The claimed group of compounds are intermediates for phosphonomethoxy nucleotide analogs, and particularly esters or amindates of an antiviral phosphonomethoxy analog of formula (1a) and the salts, hydrates, tautomers and solvates thereof. Bischofberger taught PMPA, "an acyclic nucleotide analogue." Bischofberger also "evaluated a large number of potential prodrugs," and specifically taught bis (isopropyloxy carbonyl oxymethyl) PMPA.

X is N or O; R^2 independently is --H, C_1-C_{12} alkyl, C_5-C_{12} aryl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro or --OR^3 in which R^3 is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl or C_5-C_{12} aryl; R is independently --H, C_1 -C_{12} alkyl, C_5-C_{12} aryl, C_2 -C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkyenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro, --$N(R^4)_2$ or --OR^3, where R^4 independently is --H or C_2-C_8 alkyl, provided that at least one R is not H; and a is 1 when X is O, or 1 or 2 when X is N; with the proviso that when a is 2 and X is N, (a) two N-linked R groups can be taken together to form a carbocycle or oxygen-containing heterocycle, (b) one N-linked R additionally can be --OR^3 or (c) both N-linked R groups can be --H.	Bischofberger, 1. Inherent in Bischofberger's disclosure are compounds within the claimed group of intermediate compounds. Further, Bischofberger expressly taught treating animals by orally administering the drug, which inherently would include contacting the cells of the animal with the compound.

HOLY, IN LIGHT OF NOTARI AND JONES, RENDERED THE '230 PATENT OBVIOUS

In addition to being anticipated or rendered obvious by Bischofberger, the '230 patent was also obvious in light of other prior art teachings that phosphonomethoxy nucleotide analogs, including PMPA, were strong treatments for HIV and that carbonate and carbamate could be used to produce prodrugs to increase bioavailability.

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

The '230 patent concedes that "the parental compounds have the structure $AOCH_2P(O)(OH)_2$ [and they were] well known and have demonstrated antiviral activity." '230 patent, 3:67 – 4:2. Several references confirm this concession regarding the advanced state of the art relating to phosphonomethoxy nucleotide analogs as treatments for HIV/AIDS before the filing of the '230 patent application.

First, EP 0206459 to Holy et al. published on December 30, 1986 ("Holy") and therefore is prior art to the '230 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 phosphonomethyoxy nucleotide analogs, and PMPA specifically, were already well known, the '230 patent application directed itself to the purported invention of contacting a cell with a compound comprising esters of antiviral phosphonomethyoxy nucleotide analogs with carbonates and/or carbamates.

Using Carbonate and Carbamate 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 '230 patent application was filed.

For example, Notari, "Prodrug Design," *Pharmaceutical Therapy*, 14:25-53 (1981) ("Notari"), is prior art to the '230 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 [and] carbamates." 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 and carbamate 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 '230 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 nucelotide prodrugs[.]

2. Thus, before the filing of the application leading to the '230 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 or carbamate as per the teachings of Notari and Jones. As such, the purported advance of the '230 patent, even if novel, would have been obvious in light of Holy, with Notari and Jones. The contacting of a cell with such a compound was a well known and obvious application of a beneficial prodrug.

The chart below sets forth an element-by-element comparison of the claim of the '230 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

the '230 patent's claim obvious. As such, the claim of the '230 patent is invalid and should be canceled.

'230 Patent	*Holy, with Notari and Jones*
1. A method comprising contacting a cell with a compound having formula (1a)  (1a) wherein Z is independently --$OC(R^2)_2OC(O)X(R)_a$, an ester, an amidate or --H, but at least one Z is --$OC(R^2)_2OC(O)X(R)_a$; A is the residue of an antiviral phosphonomethoxy nucleotide analog; X is N or O; R^2 independently is --H, C_1-C_{12} alkyl, C_5-C_{12} aryl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro or --OR^3 in which R^3 is C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl or C_5-C_{12} aryl; R is independently --H, C_1 -C_{12} alkyl, C_5-C_{12} aryl, C_2 -C_{12} alkenyl, C_2-C_{12} alkynyl, C_7-C_{12} alkyenylaryl, C_7-C_{12} alkynylaryl, or C_6-C_{12} alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro, --$N(R^4)_2$ or --OR^3, where R^4 independently is --H or C_2-C_8 alkyl, provided that at least one R is not H; and a is 1 when X is O, or 1 or 2 when X is N; with the proviso that when a is 2 and X is N, (a) two N-linked R groups can be taken together to	The claimed group of compounds are intermediates for phosphonomethoxy nucleotide analogs. Holy taught anti-viral treatments made from 9-(Phosphonylmethoxyalkyl) adenines, otherwise referred to as 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. 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 or carbamate as per the teachings of Notari and Jones. It is inherent in the teachings of each of Holy, Notari and Jones, that such compounds would be used in a method comprising contacting a cell with the compounds, because the express purpose of the compounds is to treat animals or humans infected with a virus, which can only be accomplished by contacting the cells of the

form a carbocycle or oxygen-containing heterocycle, (b) one N-linked R additionally can be --OR^3 or (c) both N-linked R groups can be --H.	animal with the compounds.

For these reasons, Holy, in light of Notari and Jones, rendered the claim of the '230 patent obvious. As such, the claim of the '230 patent is invalid and should be canceled.

CONCLUSION

For the reasons set forth above, the claim of the '230 patent is invalid. As such, PUBPAT respectfully requests that it 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. 6,043,230 as provided for in 37 C.F.R. § 1.33(c):

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