IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT NO.: 5,922,695

ISSUED: Jul. 13, 1999

TO: Arimilli et al.

FOR: ANTIVIRAL PHOSPHONOMETHYOXY 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. 5,922,695 issued July 13, 1999, to Arimilli et al. and assigned to Gilead Sciences, Inc. ("the '695 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 '695 patent is attached hereto as Appendix A.

THE '695 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 '695 patent claims compounds comprising esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates, which are useful as intermediates for the preparation of PMPA. The '695 patent also claims methods of orally administering such phosphonomethoxy nucleotide analogs to patients infected with HIV.

Gilead is using the '695 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 '695 patent being used to deny American

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").

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 '695 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 '695 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 – 31 of the '695 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 – 31 of the '695 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: 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 '695 patent application. A detailed explanation of the pertinency and manner of applying the cited patents and publications to the claims of the '695 patent is set forth below.[4]

BISCHOFBERGER ANTICIPATED OR RENDERED OBVIOUS THE '695 PATENT

The '695 patent application was filed July 25, 1997. It claims priority as a continuation-in-part to a provisional application – No. 60/022,708 – filed July 26, 1996 ("the '708 application"). However, the 31 claims of the '695 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 31 claims of the '695 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 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

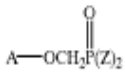
4 Appendix B contains a copy of the cited patents and publications.

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).

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 '695 patent contains 31 claims, only 1 of which is independent. That claim, Claim 1, states:

> 1. 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;
and the salts, hydrates, tautomers and solvates thereof.

The other 30 claims depend from claim 1 and are directed to more specific compounds or methods of preparing such compounds, except claim 25, which is directed to orally administering to a patient infected with a virus a compound of claim 1.

The '708 application did not satisfy the written description requirement with respect to the '695 patent's 31 claims because they all rely on claim 1's "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. Further, the '695 patent specification contains a significant discussion of salts that did not appear in the '708 application specification. '695 patent, 3:33-63.

Yet another example of the significant differences between the specification of the '695 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 '695 patent between 6:53 and 32:56 that are completely absent from the '708 application's specification. That is well over *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 '695 patent are illustrated in Table 1 below.

Differences	***'695 Patent***	***'708 Application***
Formula 1(a)	 (1a) 60:2-7.	$A(Z)_n$ (1a) 36:5.
Discussion of Salts	3:33-63.	Does not exist.
Specific Examples	Numerous formulas and specific compound embodiments. 6:53 - 32:56.	Does not exist.

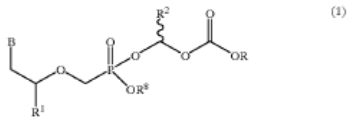
TABLE 1: Differences Between Specifications of '695 Patent and '708 Application

Since each of these topics are critical to the claims of the '695 patent, the substantial difference in disclosure about them between the specifications of the '708 application and the '695 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 '695 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 the filing of the '695 patent application on July 25, 1997.

As such, since Bischofberger was published January 22, 1997, it is prior art to the 31 claims of the '695 patent under 35 U.S.C. § 102(a). The chart below sets forth an element-by-element comparison of all 31 claims of the '695 patent to the teaching of Bischofberger. In essence, Bischofberger taught PMPA and bis(POC)PMPA, which is the focus of the '695 patent's disclosure and claims. '695 patent, 44:64 – 45:66 (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 '695 patent's 31 claims, each of those elements are nonetheless either inherent in or rendered obvious by Bischofberger's teachings. Therefore, each claim of the '695 patent is invalid and should be canceled.

'695 Patent	***Bischofberger***
1. 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,	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. Bischofberger, 1. Inherent in Bischofberger's disclosure are compounds within the claimed group of intermediate compounds.

--$N(R^4)_2$ 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; and the salts, hydrates, tautomers and solvates thereof.	
2. The compound of claim 1 having formula (1)  (1) wherein B is guanin-9-yl, adenin-9-yl, 2,6-diaminopurin-9-yl, 2-aminopurin-9-yl or their 1-deaza, 3-deaza, or 8-aza analogs, or B is cytosin-1-yl; 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} 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^1 is hydrogen, --CH_3, --CH_2OH, --CH_2F, --$CH{=}CH_2$, or --CH_2N_3, or R^1 and R^8 are joined to form --CH_2--; R^2 independently is hydrogen or C_1-C_6 alkyl; and R^8 is hydrogen or --CHR^2 --O--C(O)--OR, or	The claimed group of compounds are intermediates for phosphonomethoxy nucleotide analogs. Bischofberger taught PMPA, “an acyclic nucleotide analogue." Bischofberger also "evaluated a large number of potential prodrugs," and specifically taught bis (isopropyloxy carbonyl oxymethyl) PMPA. Bischofberger, 1. Inherent in Bischofberger's disclosure are compounds within the claimed group of compounds.

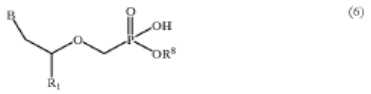
R^8 is joined with R^1 to form --CH_2 --; and the salts, hydrates, tautomers and solvates thereof.	
3. The compound of claim 2 wherein R^2 is --H.	As discussed above, the claim 2 compounds were obvious. The additional limitation that R^2 is --H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
4. The compound of claim 3 wherein R^1 is --CH_3.	As discussed above, the claim 3 compounds were obvious. The additional limitation that R^1 is --CH_3 is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
5. The compound of claim 1 wherein R^2 is --H.	As discussed above, the claim 1 compounds were obvious. The additional limitation that R^2 is --H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
6. The compound of claim 1 wherein one R^2 is --CH_3 and the other R^2 is H.	As discussed above, the claim 1 compounds were obvious. The additional limitation that one R^2 is --CH_3 and the other R^2 is H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
7. The compound of claim 1 wherein R^3 is C_1-C_6 alkyl or phenyl.	As discussed above, the claim 1 compounds were obvious. The additional limitation that R^3 is C_1-C_6 alkyl or phenyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.

8. The compound of claim 1 wherein R^3 is --CH_3 or --C_2H_5.	As discussed above, the claim 1 compounds were obvious. The additional limitation that R^3 is --CH_3 or --C_2H_5 is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
9. The compound of claim 1 wherein X is O.	As discussed above, the claim 1 compounds were obvious. The additional limitation that X is O is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
10. The compound of claim 1 wherein X is N and one R^3 is H.	As discussed above, the claim 1 compounds were obvious. The additional limitation that X is N and one R^3 is H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
11. The compound of claim 4 wherein the compound is enriched or resolved at the carbon atom chiral center linked to R^1.	As discussed above, the claim 4 compounds were obvious. The additional limitation that the compound is enriched or resolved at the carbon atom chiral center linked to R^1 is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
12. The compound of claim 4 wherein at least about 90% of the compound is in the (R) configuration at the R^1 site.	As discussed above, the claim 4 compounds were obvious. The additional limitation that at least about 90% of the compound is in the (R) configuration at the R^1 site is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
13. The compound of claim 12 wherein B is adenin-9-yl.	As discussed above, the claim 12 compounds were obvious. The additional limitation that B is adenin-9-yl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.

14. The compound of claim 13 wherein each R is ethyl.	As discussed above, the claim 13 compounds were obvious. The additional limitation that each R is ethyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
15. The compound of claim 13 wherein each R is isopropyl.	As discussed above, the claim 13 compounds were obvious. The additional limitation that each R is isopropyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
16. The compound of claim 13 wherein each R is 3-pentyl or neopentyl.	As discussed above, the claim 13 compounds were obvious. The additional limitation that each R is 3-pentyl or neopentyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
17. The compound of claim 13 wherein each R is t-butyl or isobutyl.	As discussed above, the claim 13 compounds were obvious. The additional limitation that each R is t-butyl or isobutyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
18. The compound of claim 4 wherein B is 2,6-diaminopurin-9-yl.	As discussed above, the claim 4 compounds were obvious. The additional limitation that B is 2,6-diaminopurin-9-yl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
19. The compound of claim 3 wherein R^1 is H.	As discussed above, the claim 4 compounds were obvious. The additional limitation that R^1 is H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.

20. The compound of claim 19 wherein B is adenin-9-yl.	As discussed above, the claim 19 compounds were obvious. The additional limitation that B is adenin-9-yl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
21. The compound of claim 4 wherein R is C_1 -C_{12} alkyl.	As discussed above, the claim 4 compounds were obvious. The additional limitation that R is C_1-C_{12} alkyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
22. The compound of claim 3 wherein R^1 is --CH_2 OH.	As discussed above, the claim 3 compounds were obvious. The additional limitation that R^1 is --CH_2 OH is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
23. The compound of claim 22 wherein B is cytosin-1-yl.	As discussed above, the claim 22 compounds were obvious. The additional limitation that B is cytosin-1-yl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
24. The compound of claim 22 wherein at least about 90% of the compound is in the (S) configuration at the R^1 site.	As discussed above, the claim 22 compounds were obvious. The additional limitation that at least about 90% of the compound is in the (S) configuration at the R^1 site is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.

25. A method comprising orally administering to a patient infected with virus or at risk to viral infection a therapeutically effective amount of a compound of claim 1.	Bischofberger taught increasing "oral bioavailability of PMPA," and that "Bis(POC)PMPA is a promising agent for the treatment and prophylaxis of HIV infections." Inherent in these teachings is that a therapeutically effective amount of bis(POC)PMPA was orally administered to patients infected with HIV, a virus. The claim 1 compounds are intermediates for phosphonomethoxy nucleotide analogs. Bischofberger taught PMPA, "an acyclic nucleotide analogue." Bischofberger also "evaluated a large number of potential prodrugs," and specifically taught bis (isopropyloxy carbonyl oxymethyl) PMPA. Bischofberger, 1. Inherent in Bischofberger's disclosure are compounds within the claimed group of compounds.
26. A method for preparing a compound of formula (1a) of claim 1 comprising reacting the diacid of a phosphonomethoxy nucleotide analog with L--CH(R^2)OC(O)X$(R)_n$ wherein L is a leaving group.	The claim 1 compounds are intermediates for phosphonomethoxy nucleotide analogs. Bischofberger taught PMPA, "an acyclic nucleotide analogue." Bischofberger also "evaluated a large number of potential prodrugs," and specifically taught bis (isopropyloxy carbonyl oxymethyl) PMPA. Bischofberger, 1. Inherent in Bischofberger's disclosure of compounds within the claimed group of compounds is a method for preparing such compounds. The particular method for preparing such compounds claimed would have been obvious to one of ordinary skill in the art.

27. A method for preparing a compound of formula (1) of claim 2 comprising reacting a compound of formula (6)  (6) with L--CHR^2 --O--C(O)--OR and recovering a compound of formula (1), wherein B is guanin-9-yl, adenin-9-yl, 2,6-diaminopurin-9-yl, 2-aminopurin-9-yl or their 1-deaza, 3-deaza, or 8-aza analogs, or B is cytosin-1-yl; R^1 is hydrogen, --CH_3, --CH_2OH, --CH_2F, --$CH{=}CH_2$, --CH_2N_3 or R^1 and R^8 are joined to form --CH_2--; and R^8 is hydrogen, --CHR^2 --O--C(O)--OR or R^8 is joined with R^1 to form --CH_2--; and R^2 is H, C_1-C_{12} alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is unsubstituted or is substituted with halo, azido, nitro or OR^3 in which R^3 is C_1-C_{12} alkyl; R is independently H, C_1-C_{12} alkyl, aryl, alkenyl, alkynyl, alkenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is unsubstituted or is substituted with halo, azido, nitro or OR^3, provided that at least one R is not H; and L is a leaving group.	The claim 2 compounds are intermediates for phosphonomethoxy nucleotide analogs. Bischofberger taught PMPA, "an acyclic nucleotide analogue." Bischofberger also "evaluated a large number of potential prodrugs," and specifically taught bis (isopropyloxy carbonyl oxymethyl) PMPA. Bischofberger, 1. Inherent in Bischofberger's disclosure of compounds within the claimed group of compounds is a method for preparing such compounds. The particular method for preparing such compounds claimed would have been obvious to one of ordinary skill in the art.
28. The method of claim 27 comprising conducting the reaction using at least about 1.0 equivalent of L--CHR^2 --O--C(O)--OR.	As discussed above, the claim 27 method was obvious. Conducting the reaction using at least about 1.0 equivalent of L--CHR^2 --O--C(O)–OR is a predictable step that could be used in that method and provides no unexpected superior results. Thus, it, too, was obvious.

29. The method of claim 27 comprising conducting the reaction in the presence of an organic base in an organic solvent at a reaction temperature of about 4-100° C. for about 4-72 hours.	As discussed above, the claim 27 method was obvious. Conducting the reaction in the presence of an organic base in an organic solvent at a reaction temperature of about 4-100° C. for about 4-72 hours is a predictable step that could be used in that method and provides no unexpected superior results. Thus, it, too, was obvious.
30. The method of claim 27 wherein the compound of formula (1) is recovered by forming a salt, precipitating the salt and recovering the precipitated salt.	As discussed above, the claim 27 method was obvious. Recovering the compound by forming a salt, precipitating the salt and recovering the precipitated salt is a predictable step that could be used in that method and provides no unexpected superior results. Thus, it, too, was obvious.
31. The method of claim 30 wherein the salt is formed from sulfuric acid, phosphoric acid, lactic acid, or citric acid.	As discussed above, the claim 30 method was obvious. Forming the salt from sulfuric acid, phosphoric acid, lactic acid, or citric acid is a predictable step that could be used in that method and provides no unexpected superior results. Thus, it, too, was obvious.

HOLY, IN LIGHT OF NOTARI AND JONES, RENDERED THE '695 PATENT OBVIOUS

In addition to being anticipated or rendered obvious by Bischofberger, the '695 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 '695 patent concedes that "the parental compounds have the structure

$AOCH_2P(O)(OH)_2$ [and they were] well known and have demonstrated antiviral activity." '695 patent, 3:65-66. 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 '695 patent application.

First, EP 0206459 to Holy et al. published on December 30, 1986 ("Holy") and therefore is prior art to the '695 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 '695 patent application directed itself to the purported invention of compounds comprising esters of antiviral phosphonomethyoxy nucleotide analogs with carbonates and/or carbamates. The '695 patent argued that such "novel" compounds were "useful as intermediates for the preparation of antiviral compounds."

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 '695 patent application was filed.

For example, Notari, "Prodrug Design," *Pharmaceutical Therapy*, 14:25-53 (1981) ("Notari"), is prior art to the '695 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 '695 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[.]

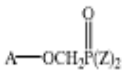
2. Thus, before the filing of the application leading to the '695 patent, those of ordinary skill in the art were already motivated to develop prodrugs of nucleotide analogs. Jones further disclosed the successful creation of an ester prodrug from PMEA, which is structurally similar to PMPA. 5.

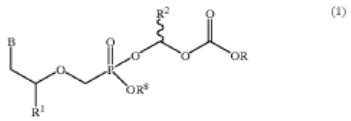
Thus, one of ordinary skill in the art would have been motivated by Notari to produce prodrugs for Holy's antiviral nucleotide analogs because they were taught by Jones to have limited bioavailability and because Jones specifically cited Holy. Jones, 2. One of ordinary skill in the art would have also 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 '695 patent, even if novel, would have been obvious in light of Holy, with Notari and Jones.

The dependent claims 2-31 of the '695 patent are simply directed to the selection and preparation of esters from a group of prodrug linkages that were also well known and practiced in the prior art in order to improve the bioavailability of parent compounds or to method for preparing such compounds, which were well know methods at the time the '695 patent priority application was filed. Thus, they, too, were obvious in light of Holy with Notari and Jones.

The chart below sets forth an element-by-element comparison of all 31 claims of the

'695 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 nucleoside and nucleotide analogs, rendered each of the '695 patent's claims obvious. As such, each claim of the '695 patent is invalid and should be canceled.

'695 Patent	***Holy, with Notari and Jones***
1. A compound having formula (1a)  (1a) wherein Z is independently --OC(R^2)$_2$OC(O)X(R)$_a$, an ester, an amidate or --H, but at least one Z is --OC(R^2)$_2$OC(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,	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.

--$N(R^4)_2$ 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; and the salts, hydrates, tautomers and solvates thereof.	
2. The compound of claim 1 having formula (1)  (1) wherein B is guanin-9-yl, adenin-9-yl, 2,6-diaminopurin-9-yl, 2-aminopurin-9-yl or their 1-deaza, 3-deaza, or 8-aza analogs, or B is cytosin-1-yl; 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} 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^1 is hydrogen, --CH_3, --CH_2OH, --CH_2F, --$CH{=}CH_2$, or --CH_2N_3, or R^1 and R^8 are joined to form --CH_2--; R^2 independently is hydrogen or C_1-C_6 alkyl; and R^8 is hydrogen or --CHR^2 --O--C(O)--OR, or	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.

R^8 is joined with R^1 to form --CH_2 --; and the salts, hydrates, tautomers and solvates thereof.	
3. The compound of claim 2 wherein R^2 is --H.	As discussed above, the claim 2 compounds were obvious. The additional limitation that R^2 is --H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
4. The compound of claim 3 wherein R^1 is --CH_3.	As discussed above, the claim 3 compounds were obvious. The additional limitation that R^1 is --CH_3 is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
5. The compound of claim 1 wherein R^2 is --H.	As discussed above, the claim 1 compounds were obvious. The additional limitation that R^2 is --H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
6. The compound of claim 1 wherein one R^2 is --CH_3 and the other R^2 is H.	As discussed above, the claim 1 compounds were obvious. The additional limitation that one R^2 is --CH_3 and the other R^2 is H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
7. The compound of claim 1 wherein R^3 is C_1-C_6 alkyl or phenyl.	As discussed above, the claim 1 compounds were obvious. The additional limitation that R^3 is C_1-C_6 alkyl or phenyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.

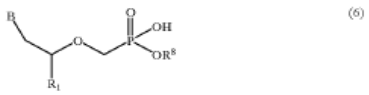
8. The compound of claim 1 wherein R^3 is --CH_3 or --C_2H_5.	As discussed above, the claim 1 compounds were obvious. The additional limitation that R^3 is --CH_3 or --C_2H_5 is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
9. The compound of claim 1 wherein X is O.	As discussed above, the claim 1 compounds were obvious. The additional limitation that X is O is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
10. The compound of claim 1 wherein X is N and one R^3 is H.	As discussed above, the claim 1 compounds were obvious. The additional limitation that X is N and one R^3 is H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
11. The compound of claim 4 wherein the compound is enriched or resolved at the carbon atom chiral center linked to R^1.	As discussed above, the claim 4 compounds were obvious. The additional limitation that the compound is enriched or resolved at the carbon atom chiral center linked to R^1 is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
12. The compound of claim 4 wherein at least about 90% of the compound is in the (R) configuration at the R^1 site.	As discussed above, the claim 4 compounds were obvious. The additional limitation that at least about 90% of the compound is in the (R) configuration at the R^1 site is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
13. The compound of claim 12 wherein B is adenin-9-yl.	As discussed above, the claim 12 compounds were obvious. The additional limitation that B is adenin-9-yl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.

14. The compound of claim 13 wherein each R is ethyl.	As discussed above, the claim 13 compounds were obvious. The additional limitation that each R is ethyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
15. The compound of claim 13 wherein each R is isopropyl.	As discussed above, the claim 13 compounds were obvious. The additional limitation that each R is isopropyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
16. The compound of claim 13 wherein each R is 3-pentyl or neopentyl.	As discussed above, the claim 13 compounds were obvious. The additional limitation that each R is 3-pentyl or neopentyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
17. The compound of claim 13 wherein each R is t-butyl or isobutyl.	As discussed above, the claim 13 compounds were obvious. The additional limitation that each R is t-butyl or isobutyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
18. The compound of claim 4 wherein B is 2,6-diaminopurin-9-yl.	As discussed above, the claim 4 compounds were obvious. The additional limitation that B is 2,6-diaminopurin-9-yl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
19. The compound of claim 3 wherein R^1 is H.	As discussed above, the claim 4 compounds were obvious. The additional limitation that R^1 is H is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.

20. The compound of claim 19 wherein B is adenin-9-yl.	As discussed above, the claim 19 compounds were obvious. The additional limitation that B is adenin-9-yl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
21. The compound of claim 4 wherein R is C_1 -C_{12} alkyl.	As discussed above, the claim 4 compounds were obvious. The additional limitation that R is C_1-C_{12} alkyl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
22. The compound of claim 3 wherein R^1 is --CH_2 OH.	As discussed above, the claim 3 compounds were obvious. The additional limitation that R^1 is --CH_2 OH is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
23. The compound of claim 22 wherein B is cytosin-1-yl.	As discussed above, the claim 22 compounds were obvious. The additional limitation that B is cytosin-1-yl is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.
24. The compound of claim 22 wherein at least about 90% of the compound is in the (S) configuration at the R^1 site.	As discussed above, the claim 22 compounds were obvious. The additional limitation that at least about 90% of the compound is in the (S) configuration at the R^1 site is an obvious sub-genus of those compounds that provides no unexpected superior results. Thus, it, too, was obvious.

25. A method comprising orally administering to a patient infected with virus or at risk to viral infection a therapeutically effective amount of a compound of claim 1.	The claim 1 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. Further, Jones and Notari expressly taught that such prodrugs are administered orally. Jones, 4; Notari, 26.

26. A method for preparing a compound of formula (1a) of claim 1 comprising reacting the diacid of a phosphonomethoxy nucleotide analog with L--CH(R^2)OC(O)X(R)$_n$ wherein L is a leaving group.	The claim 1 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.

27. A method for preparing a compound of formula (1) of claim 2 comprising reacting a compound of formula (6)  (6) with L--CHR^2 --O--C(O)--OR and recovering a compound of formula (1), wherein B is guanin-9-yl, adenin-9-yl, 2,6-diaminopurin-9-yl, 2-aminopurin-9-yl or their 1-deaza, 3-deaza, or 8-aza analogs, or B is cytosin-1-yl; R^1 is hydrogen, --CH_3, --CH_2OH, --CH_2F, --$CH{=}CH_2$, --CH_2N_3 or R^1 and R^8 are joined to form --CH_2--; and R^8 is hydrogen, --CHR^2 --O--C(O)--OR or R^8 is joined with R^1 to form --CH_2--; and R^2 is H, C_1-C_{12} alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is unsubstituted or is substituted with halo, azido, nitro or OR^3 in which R^3 is C_1-C_{12} alkyl; R is independently H, C_1-C_{12} alkyl, aryl, alkenyl, alkynyl, alkenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is unsubstituted or is substituted with halo, azido, nitro or OR^3, provided that at least one R is not H; and L is a leaving group.	The claim 2 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.
28. The method of claim 27 comprising conducting the reaction using at least about 1.0 equivalent of L--CHR^2 --O--C(O)--OR.	As discussed above, the claim 27 method was obvious. Conducting the reaction using at least about 1.0 equivalent of L--CHR^2 --O--C(O)–OR is a predictable step that could be used in that method and provides no unexpected superior results. Thus, it, too, was obvious.

29. The method of claim 27 comprising conducting the reaction in the presence of an organic base in an organic solvent at a reaction temperature of about 4-100° C. for about 4-72 hours.	As discussed above, the claim 27 method was obvious. Conducting the reaction in the presence of an organic base in an organic solvent at a reaction temperature of about 4-100° C. for about 4-72 hours is a predictable step that could be used in that method and provides no unexpected superior results. Thus, it, too, was obvious.
30. The method of claim 27 wherein the compound of formula (1) is recovered by forming a salt, precipitating the salt and recovering the precipitated salt.	As discussed above, the claim 27 method was obvious. Recovering the compound by forming a salt, precipitating the salt and recovering the precipitated salt is a predictable step that could be used in that method and provides no unexpected superior results. Thus, it, too, was obvious.
31. The method of claim 30 wherein the salt is formed from sulfuric acid, phosphoric acid, lactic acid, or citric acid.	As discussed above, the claim 30 method was obvious. Forming the salt from sulfuric acid, phosphoric acid, lactic acid, or citric acid is a predictable step that could be used in that method and provides no unexpected superior results. Thus, it, too, was obvious.

For these reasons, Holy, in light of Notari and Jones, rendered every claim of the '695 patent obvious. As such, each claim of the '695 patent is invalid and should be canceled.

CONCLUSION

For the reasons set forth above, each of the claims of the '695 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. 5,922,695 as provided for in 37 C.F.R. § 1.33(c):

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