

**The Patents (Amendment) Act, 2005
And
The Patents (Amendment) Rules, 2006**

In the matter of application No. 602/DEL/2007
Filed on 20/03/2007
In the matter of representation filed u/s 25(1)
And
In the matter of hearing held u/s 14

M/s Gilead Sciences Inc., USA -----Applicant
M/s Cdymax (India) Pharma Ltd., Bangalore, Karnataka, India --- Opponent

Hearing held on 6/04/2011 and 02/05/2011

Present –

Mr. G. Natraj
Of Subramaniam, Natraj and Associates, New Delhi---Agent of the applicant

Mr S Majumdar, Ms Mythill Venkatesh, Ms Amrita Majumdar, Ms Shivani Srivastava
Of S, Majumdar and Co., New Delhi-----Agent of the Opponent

Dr Jyoti Verma, Examiner of Patents and Designs

Decision

1. An application titled, ‘Nucleotide analogs’ was filed on 20/03/2007 by M/s Subramaniam, Natraj and Associates, New Delhi on behalf of M/s Gilead Sciences Inc., USA as divisional application of 2076/DEL/1997 dated 25/07/1997 which claims priority of USA application no.’s 08/686,838 and 60/022,708 dated 26/07/1996. The instant application was published u/s 11A on 03/08/2007.
2. The subject matter of the instant application relates to intermediates for phosphonmethoxy nucleotide analogs of formula 1a and had 35 claims at the time of filing the application. The claims 1 to 25 were product claims for the formula 1a; claims 26 to 31 were process claims for preparation of formula 1a; and claims 32 to 35 were the omnibus claims thereof.
3. The first examination report (FER) was issued on 19/11/2009 with objections of lacking inventive step u/s 2(1)(j); new form/new use of known thing u/s 3(d) and non-allowability of the application u/s 16 for filing identical set of claims as were in the parent application. The reply to the FER was filed on 04/11/2010. There were no amendments in the claims.
4. A representation u/s 25(1) was filed on 22/09/2009 by M/s S. Majumdar and Co., New Delhi on behalf of M/s Intermed Labs Pvt. Ltd., Karnataka, India. The opponent’s name was changed to Cdymax (India) Pharma Ltd. Through petition dated 02/04/2011. A copy of the said

representation was forwarded to the applicant on 04/12/2009 giving them three months time period for filing reply statement u/s 55(4) of the Patents (Amendment) Rules, 2006. The applicant's agent filed the reply statement on 04/03/2010. Hearing u/s 14 and 25(1) was scheduled for 06/04/2011. On the very day, Mr. G Natraj, agent of the applicant, requested for adjournment of the hearing for appearing in High court in respect of some case. Considering his request, it was decided that opponent's agent will place his case on the same day and Mr. Natraj was given further date 02/05/2011 for placing his arguments.

5. At the outset, the objection raised in para 3 and 4 of FER regarding non-allowability of the instant application u/s 16 due to identical set of claims in both the parent and the divisional application is being discussed.

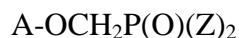
5.1 The parent application 2076/DEL/1997 dated 25/07/1997 claimed the similar compounds of formula 1a and method of preparation thereof. A representation u/s 25(1) was filed for the said application and the controller refused the application on merits of the representation.

5.2 The agent of the applicant submitted that in accordance with section 16(1), a divisional application can be filed by the applicant either suo moto or with the view to remedy the objection raised by the controller on the grounds of distinct invention. The parent application has not been granted and the instant application was filed suo moto by the applicant. The applicant's agent further submitted that in assessment of the claims in divisional, there should be no commonality of claims between those granted in the parent application and those prosecuted in a divisional application.

5.2 Discussion and decision on the issue

5.2.1 The main claim of the instant application is as follows –

1. A compound having formula (1a)



wherein Z is independently -OC(R₂)₂OC(O)X(R)_a, an ester, an amidate or H, but at least one Z is -OC(R₂)₂OC(O)X(R)_a;

A is the residue of an antiviral phosphonmetboxy nucleotide analog; X is N or O;

R₂ independently is -H, C₁-C₁₂ alkyl, C₅-C₁₂ aryl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₇-C₁₂ alkenylaryl, C₇-C₁₂ alkynylaryl, or C₆-C₁₂ alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro or -OR₃ in which R₃ is C₅-C₁₂alkyl, C₅-C₁₂ alkenyl, C₅-C₁₂alkynyl or C₅-C₁₂ aryl;

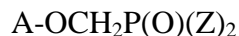
R is independently -H, C₅-C₁₂ alkyl, C₅-C₁₂ aryl, C₂-C₁₂ alkenyl, C₂-C₁₂ alkynyl, C₇-C₁₂ alkenylaryl, C₇-C₁₂ alkynylaryl, or C₆-C₁₂ alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro, -N(R₄)₂ or -OR₃ where which R₄ independently is -H or C₁-C₈ alkyl, provided 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 -OR3 or (c) both N-linked R groups can be-H; and the salts, hydrates tautomers and solvates thereof.

5.2.2 All the other claims are effectively dependent on said claim 1.

5.2.3 The main claim of the said parent application is as follows –

1.A compound having formula (1a)



wherein Z is independently -OC(R2)2OC(O)X(R)a, an ester, an amidate or H, but at least one Z is -OC(R2)2OC(O)X(R)a;

A is the residue of an antiviral phosphonmetboxy nucleotide analog; X is N or O;

R2 independently is -H, C1-C12 alkyl, C5-C12 aryl, C2-C12 alkenyl, C2-C12alkynyl, C7-C12 alkenylaryl, C7-C12 alkynylaryl, or C6-C12 alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro or-OR3 in which R3 is C5-C12alkyl, C5-C12 alkenyl,C5-C12alkynyl or C5-C12 aryl;

R is independently -H, C5-C12 alkyl, C5-C12 aryl, C2-C12 alkenyl, C2-C12 alkynyl, C7-C12 alkenylaryl, C7-C12 alkynylaryl, or C6-C12 alkaryl, any one of which is unsubstituted or is substituted with 1 or 2 halo, cyano, azido, nitro, -N(R4)2 or- OR3 where which R4 independently is -H or C1-C8 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 -OR3 or (c) both N-linked R groups can be-H;

and the salts, hydrates tautomers and solvates thereof.

5.2.4 It is clear that the claims of both the parent and divisional applications are same.

5.2.5 Section 16(3) of the Act states that:

Section 16(3): The Controller may require such amendment of the complete specification filed in pursuance of either the original or the further application as may be necessary to ensure that neither of the said complete specifications includes a claim, for any matter claimed in the other.

5.2.6 According to this section, the Patent Act does not permit the refiling of the same claims in divisional as were in the parent application which were existing on the final date as mentioned in section 21(1). In this case the parent application was refused on 30/07/2009 on merits of the representation u/s 25(1). The applicant cannot refile the refused claims in a divisional application as section 16(1) and 16(3) puts a bar on such type of reclaiming. Allowance of refiling of such claims in the form of a divisional application will amount to

extension of the time limit of section 21(1) and reexamination of the same claims by the Patent office which was refused at a previous date.

5.2.7 Section 16(1) of the Patent Act clearly stipulates that the applicant may file a divisional application if “the claims of the complete specification relate to more than one invention,”

In this case the parent specification does not refer to multiple set on inventions; therefore the applicants were not entitled to file a divisional application on the claims of parent application.

5.2.8 Further, the claims of any application if refused, comes into the public domain for free use and, therefore allowing reclaiming of same claims in the form of a divisional application shall be against the public interest as patentee of such divisional application shall be entitled to file infringement suit against the user of that already refused claims.

5.2.9 Hon'ble Supreme Court of India in Ramdev Food Products Pvt. Ltd. Vs. Arvindbhai Rambhai Patel and Ors. [(2006)8SCC726]

“It is well-settled that what cannot be done directly cannot be done indirectly.”

5.2.10 Decision on the issue -

In view of the above said, the arguments placed by the applicant’s agent are not acceptable. The objection raised by the office at para 3 and 4 of the FER cannot be waived off. Therefore the instant application cannot be considered as a divisional application u/s 16 and is refused for grant of patent.

The instant application cannot even exist as an independent application as the same set of claims have already been published before priority date in the patent office journal dated 11/03/2005.

6. Notwithstanding the discussion of para 5, the merits of the representation is being discussed. The opponents took the following grounds of section 25(1) at the time of hearing –

1. Section 25(1)(e) - Lack of inventive step
2. Section 25(1)(f) - Not an invention u/s 3(d)

6.1 The opponent relied upon the following documents –

- D1 – WO 95/07920 (Publication date March 23, 1995)
- D2 – C W Thomber ‘Isosterism and molecular modification in drug design’, Chem. Soc. Reviews, 18 (1979), 563-580
- D3 – US 4816570 (Publication date March 28, 1989)
- D4 – US 4968788 (Publication date November 6, 1990)
- D5 – US 5177064 (Publication date January 5, 1993)
- D6 – Notari et al, Prodrug Design, Pharmaceutical Therapy, 14: 25-53 (1981)
- D7 – WO 1994/03467 (Publication date February 17, 1994)

D8 – Serafinowska et al, 'Synthesis and in vivo evaluation of prodrugs of 9-[2-(phosphonomethoxy) ethoxy] adenine', J. Med. Chem., 1995, 38, 1372-1379

D9 – Starrett et al., 'Synthesis, oral bioavailability determination and in vitro evaluation of prodrugs of the antiviral agent 9-[2-(phosphonomethoxy) ethyl] adenine (PMEA), J. Med. Chem., 1994, 37, 1857-1864

7. Section 25(1)(e) - Lack of inventive step

The opponent's agent submitted the following –

7.1 D1 relates to novel nucleotide analog amidates and esters, their pharmaceutically acceptable acid addition salts, a process for their production and their use. Disclosure of D1 as highly relevant because the parental compounds of the present application having structure **AOCH₂P(O)(OH)₂** and those of the prior art D1 are both phosphonates. The opponent's agent referred to page 2, lines 3-9, 20-23; page 3, lines 4-14; page 6; page 9, lines 4-10, 11-19 and last paragraph; page 25, table 1, second column; page 21, lines 13-18; page 25, table 1.

7.2 D2 establishes that 'O', 'NH' and 'CH₂' are known as isosteric equivalents (page 564, table 1, serial number 2). Page 567, paragraph 3, first sentence of D2 disclose that bioisosteric replacements are useful in searching for potency, selectivity, absorption and duration.

7.3 D3 provides protective groups that are specifically suitable for masking phosphates and phosphonates and the mechanism of demasking of the prodrugs. D3 discusses that if the parent is unstable under the relevant biological conditions, it can be derivatized with protective groups which will create a more stable product. The protective groups can be selected so that they will be removed under predetermined biological conditions that exist at the site in the system where the parent is needed. D3 teaches that the phosphoesters (phosphomonoesters and phosphodiester) have very substantial therapeutic potential, but thus far they have not been practically useful, because they usually cannot penetrate cell membranes. There are two reasons for this penetration problem. First, these phosphoesters are negatively charged at physiologic pH and are highly hydrophilic. Consequently, they are chemically incompatible with lipid membranes. Second, most of these compounds are rapidly degraded by enzymes in the blood and on cell surfaces.

7.4 Column 3, lines 25-32 teaches that carbamate group is much preferred protecting group for phosphate and phosphonate containing active agents. Column 3, lines 40 - 45 clearly teaches that suitable active agents include compounds wherein the heterocyclic base (R₂) includes nucleosid-5'-yl groups such as 2'-deoxynucleosid-5'-yl groups and analogs thereof. Lines 45-50, column 3 of D3 specifically teaches that these protected compositions (i.e. compounds) are resistant to the blood and cell surface enzymes that degrade the parent phosphates.

7.5 Column 4, lines 18-27 of D3 is as hereunder:

'The R_i and R₃ substituents on these two types of protective groups can be modified to give the masked composition almost any desired physical or chemical property. By thus controlling the properties of the protected composition, variables such as location and rate of demasking can be controlled. This method has potential applications in modulating biochemical pathways,

abrogating metabolic deficiencies, circumventing resistance to anticancer drugs and developing new anticancer, antiviral, and antiparasitic drugs'

7.6 Disclosure of D4 is similar to that of D3. The definition of XI provided in lines 23-25, column 3 of D4 includes H and R1COOCR23, such that the other hydroxyl of the phosphonate group may be left unprotected. The opponent states that the definition of Z provided in claim 1 of the instant application stipulates that at least one of the hydroxyl groups is protected while the other hydroxyl group may be left unprotected. Therefore, this feature of the claims is taught by the disclosure of D4.

7.7 Column 28, lines 17-27 of D5 shows that the backbone heterocyclic bases of the compounds of D5 are same as that of the compounds of the instant application. The protected phosphonate moiety disclosed in D5 have the structure wherein

R1 is C1 -C8 alkyl, C6 -C10 aryl or C7 -C12 aralkyl;

R2 is hydrogen, Ci -Cg alkyl, C6 -C10 aryl, etc.; and

R3 is selected from the group consisting of, among others, alkoxy having 1 to 4 carbon atoms (carbonate prodrug) and dialkylamino having 2 to 8 carbon atoms (carbamate prodrug).

7.8 Column 18, lines 44-54 of D5 disclose the meaning and scope of the various hydroxyl protecting groups. Column 18, line 55 of D5 teaches that typical hydroxyl protecting groups contemplated by the disclosed invention are the acyl groups and carbonates. Column 20, lines 20 - 50 discusses the various carbonates protecting groups preferred.

7.9 D6 teaches phosphates, carbonates and hemiester prodrugs.

7.10 D7 discloses the parental compounds of the instant application.

7.11 D8 reveals that the bioavailability of PME A ester and the crystalline hydrochloride salt of diphenyl ester displayed an oral bioavailability of 30% and 50% that was 15 fold and 25 fold higher than the bioavailability observed after dosing of PME A.

7.12 The abstract of D9 shows that when evaluated in vitro against HSV-2, the (acyloxy) alkyl phosphonates demonstrated greater than 200 fold activity compared with PME A per se.

The applicant's agent submitted the following –

7.13 D1 discloses various structurally defined methoxyphosphonate analogues including PMP and PME and also teaches linking defined esters or amino groups to the phosphonate hydroxyls. The esters include (acyloxy) alkyl groups. Despite disclosing a long list of esters, D1 does not teach substituting the phosphorous hydroxyl with any carbonate or carbamate. Making a bioisosteric replacements in POM type prodrugs results in structures of C/P-OC(R2)zOC(=O)R; C/P-OC(RZ)zOC(=O)OR; and C/POC(R2)2OC(=O)N(R)R. These are not carbonate prodrugs, which would typically have the structure C-OC(O)OR. This compound lacks the oxymethyl group found in the compounds of the instant application.

7.14 D2 is simply a general guidance towards research and also provides a warning that predictability of results using the principle of bioisosterism would be incorrect and that in certain cases, exactly opposite results have been obtained by the use of bioisosters. D2 discloses bivalent C(O)CH₂R, C(O)NHR, C(O)SR and C(O)OR groups as bioisosteres in drug or prodrug design. In the present invention, the corresponding groups are terminal substitutions and are not bivalent at all. D2 itself teaches that "what proves to be a good bioisosteric replacement in one series of compounds will not necessarily be useful in another" (page 566).

7.15 D3 and D4 teach away from forming carbonates or carbamates. These references actually suggest that acyloxyalkyl group is preferred over carbamate. D3 discloses prodrugs containing the (acyloxy) alkyl and/or (acyloxy) amine promoieties. The phosphonate of D3 contains a C-P bond but is otherwise completely dissimilar to the parent compounds employed in the present invention. D4 discloses phosphonates containing a C-P bond but otherwise bears no resemblance to the parent compounds employed in the present application. D4 makes only 4 carbamates out of 62 prodrugs.

7.16 D5 suggests the use of (acyloxy) alkyl as the preferred group and has no examples of carbonate or carbamate groups at all. D5 discloses linking a phosphonate to a "drug having a reactive functional group". The phosphonate is a substituting group for the drug; facilitated by the drug's possession of a "reactive functional group." the phosphonate of D5 is not the drug. It is a substituent that is in fact substituted onto the drug. In the instant application, the phosphonate is the drug.

7.17 D6 states that structural differences in prodrugs will result in changes in the form and level of cleavage of prodrugs in the body due to esterase action. D6 actually suggests that prodrugs intended to increase the oral bioavailability of a poorly absorbed drug should provide for "instantaneous system conversion of prodrug to drug" because circulating prodrug represents an inactive species which may also be eliminated intact (p. 34). D6 explicit states that the best site for prodrug reversal depends on the result sought to be achieved and that preferably, the prodrug should be converted to drug as soon as the result is achieved. D6 while it teaches towards optimization of rate differences does not provide any information to predict reasonable success in switching profunctionalities.

7.18 D8 results are not comparable with the results of the present invention Since D8 determined bis(POM)PMEA bioavailability in mice, whereas the tests in the present invention were in dogs. It is further submitted that the opponent have not shown that the methods under which the bioavailability studies were conducted in D8 and the instant invention were even remotely comparable, e.g., administration conditions, sampling times, drug assays and the like.

7.19 D9 reports that bis(acyloxyalkyl)PMEA compounds have oral bioavailability's of 17.6%, 14.6% and 15.4% (using rats rather than dogs). However, what is chosen by the opponent from D8 is a bioavailability showing of 30%. What this does establish is that choice of animal species produces a radically different bioavailability.

7.20 D9 tests PMEA derivatives against HSV2. PMPA is not even active against HSV-2. However, PMPA is active against HIV-1, and it is these results that are reported in the present

application. Secondly, D9 does not disclose selectivity index results. Thus, the prodrug could show greater activity, but if it also has increased cellular toxicity to the same degree then it offers no real clinical advantage. Selectivity index takes into account increases in toxicity resulting from greater cell permeability on the part of the prodrugs. As a result, it is submitted that D9 is essentially unreliable to assess inventive step based on results.

7.21 D9 report that no increase in activity was observed when bis(pOM)PMEA was tested in an HIV assay. Applicants' showing of unexpectedly increased selectivity is based on an HIV assay, and there they show not only substantial increases in activity but also substantial increases in selectivity.

7.22 The comparative increase in bioavailability between bis(POC)PMPA of the instant application and bis(POM)PMEA is significant since

-firstly, bis(POM)PMEA is not the appropriate compound for evaluation of an increase in efficacy, both since the targets, the mode of action, the structure are different from bis(POC)PMPA;

- Secondly, that the information on bis(POM)PMEA relied on by the opponent relates to a completely different viral assay namely HSV-2. The present invention relates to HN-1;

- thirdly, bis(POM)PMEA is reported to be no more active against HIV than its parent PMEAs;

- fourthly, the anti-HIV activity of PMPA is 0.5 micro molar as shown in the complete specification of the instant application while the anti-HIV activity of several carbonate prodrugs is 0.002, <0.001, 0.003 micro molar. Thus, effectively the average activity of the prodrugs of the instant application increases by about 313 times over that of parent compound PMPA.

8. Section 25(1)(f) - Not an invention u/s 3(d)

8.1 The opponent stated that the comparative test data furnished by the applicant does not support its contention of an "unexpected and surprising" improvement in bioavailability and potency over the parental compound that was well known in the art.

8.2 The opponent stated that the ingredients used by the process are well known according to the prior art documents D1, D3 and D6 for masking the phosphonate group of PMPA, therefore the process is also not patentable u/s 3 (d).

8.3 The opponent's agent submitted that the definition of the expression "*efficacy*" as observed by the Judges of the Hon'ble Madras High Court which reads "*the ability of a drug to produce the desired therapeutic affect*": The opponent's agent submitted that the nucleotide analogs of the instant application, however did not offer any therapeutic advantage but only advantage in terms of mode of safe delivery by masking of the parent nucleotide.

8.4 The opponent's agent relied upon the following case laws and decisions –

1."Case Law of the Boards of Appeal of the European Patent Office, Fifth Edition, December 2006" (page 121 Paragraph 2)

“The boards have repeatedly pointed out that the closest prior art for assessing inventive step is normally a prior art document disclosing subject matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural Inventive step modifications (T 606/89, T 686/91, T 834/91, T 482/92, T 298/93, T 380/93, T 59/96, T 130/96, T 650/01). A further criterion for the selection of the most promising starting point is the similarity of technical problem (see T 495/91, T 510/91, T 439/92, T 989/93, T 1203/97, T263/99).”

2. Astrazeneca UK Limited v. GM Pharma Ltd

“The opponent relied on the European Board of Appeal decision T 181/82 which held that "an effect which may be said to be unexpected can be regarded as an indication of inventive step; where comparative tests are submitted as evidence of this, there must be the closest possible structural approximation - in a comparable type of use - to the subject matter of the invention.”

“To be relevant, such comparative tests must meet certain criteria. These include the choice of a compound disclosed in the application and of a comparative substance taken from the state of the art; at the same time, the pair being compared should possess maximum similarity with regard to structure and application. Given the similar properties to be expected in view of the structural similarity of two substances, evidence of an abrupt improvement can be regarded as unexpected.”

3. European Board of Appeal decision T_1101/98

“Thus, at the priority date, the skilled person was aware from document (1) of the anticonvulsant activity of the fructopyranose sulfamate, and from document (2), that imidate derivatives of sulfonamide drugs would behave as prodrugs. In the Board's judgment, it was obvious when wanting to obtain derivatives of the fructopyranose sulfamate, while keeping the anticonvulsant activity, to combine the teachings of both these documents i.e. to make Nsulfonyl imidate derivatives of said fructopyranose sulfamate. The Appellant argued that such a combination could only be done with hindsight knowledge of the content of the application as filed. However, as the usefulness of transforming drugs into prodrugs in order to solve the type of problems solved in the instant application was already known as early as 1975 (references 1 to 3, page 2071 of document (2)), this argument cannot be accepted.”

4. Aventis Pharma vs. Lupin Pharmaceuticals, Federal Circuit, 2006-1530

“In the chemical arts, we have long held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness.”

5. Decision of Patent Office for application no. 924/DELNP/2006

“In the entire description of the invention the new therapeutic effect of the new forms is not disclosed Hence it is concluded that the new crystalline form II exhibit the same efficacy as the Documents D1 to D8.”

6. Decision of Patent Office for application no. 712/DEL/2002

“I have analyzed the results as provided by the applicants regarding improved stability of the alleged compound. I have observed that the applicants have not provided a comparative data with respect to the amorphous/parent compound of the alleged invention. Also no improvement in the therapeutic efficacy of AD as compared to its parent compound (PMEA) has been provided. In fact both the compounds (AD) is used to treat viral infections which is also the activity shown by the parent compound (PMEA). In view of above I state that the subject matter for application no. 712/DEL/2002 is not patentable under section 3(d).”

8.5 The applicant’s agent submitted that the process that is claimed also uses a new reactant containing a leaving group. The requirement of a 'new' reactant is that the reactant must be used for the first time in the claimed process. Absolute novelty is not a requirement for Section 3(d) in relation to its application to a claimed process.

8.6 The applicant’s agent refers to the following literature references in support of the efficacy of the product claimed by the claims for the instant application –

1. Satoh et al., *Chemico-Biological Interactions*, 162(2006): 195-211 (Exhibit 1).
2. Lee, W.A. and Martin, J.C, Perspectives on the Development of Acyclic Nucleotide Analogs as Antiviral Drugs, 71 *Antiviral Research* 254-259 (2006) hereinafter "Lee et al." - Exhibit 2.
3. Barditch-Crovo et al, 'Anti human immunodeficiency virus (HIV) activity, safety and pharmacokinetics of adefovir dipivoxil (9-[2-(bis-pivaloyloxymethyl)-phosphonylmethoxyethyl(adenine) in HIV infected patients', *The Journal of Infectious Disease*, 1997, 176, 406-13 – Exhibit 3
4. Louie et al, 'Determining the antiviral activity of tenofovir disproxil fumarate in treatment o naïve chronically HIV-1 infected individuals', *AIDS* 2003, 17: 1151-1156 – Exhibit 4

Satoh et al (Exhibit 1)

8.7 Exhibit 1 describes a class of potential prodrug metabolizing enzymes, the carboxyl esterases ("CarbE"), a multigene .superfamily whose products are localized in the endoplasmic reticulum of (ER) of many tissues. These enzymes catalyze the hydrolysis of a variety of drugs or prodrugs containing ester- and amide-bonds. Since ester derivatives of therapeutic agents have been used as prodrugs, CarbEs "are major determinants of the pharmacokinetic behavior of most prodrugs...“(p. 198).

8.8 The applicant’s agent submitted that Exhibit 1 establishes that even in 2006, the effect of these enzymes was not known. It would not be possible to project reasonable success in switching from one profunctionality to another.

8.9 Exhibit 1 concludes that one could screen new prodrugs in the system to predict in vivo results if one had an in vitro experimental system using purified CarbEs from mammalian cell expression systems (which is not the case here). Even with this experimental system, "such in vitro experiments may not make it possible to predict in vivo results, except in a particular case". (p. 207-8).

8.10 Applicant's agent submitted that such systems were not available at the time of this invention, no tool was available to reasonably predict success in switching profunctionalites from the (acyloxy) alkyl-type to carbonate or carbamate groups. Further, Exhibit 1 states that even *with* such a tool the results could not be extrapolated, it would have been even more difficult to obtain a basis for reasonable prediction using the relatively primitive technologies at the time this application was first filed. Clearly, uncertainty about the hydrolyzing enzyme(s) for the various profunctionalities would render the effort an invitation to experiment, and no more.

Lee et al (Exhibit 2)

8.11 Exhibit 2 is a study on the clinical benefit of administering bis(POC)PMPA fumarate ("TDF") orally as compared to intravenous or subcutaneous free PMPA ("tenofovir"). As seen in Fig. 4, of Exhibit 2, the AUC ratio of tenofovir in PBMCs compared to plasma is 4.5 after oral delivery of TDF and it is approximately 1.3 after subcutaneous delivery of tenofovir in the dog. Therefore, for the same tenofovir AUC, oral TDF will deliver more active drug to PBMCs than IV tenofovir. These data are consistent with our hypothesis of increased intracellular delivery with TDF and provide an explanation for the enhanced antiviral effect observed."

8.12 Exhibit 2 supports the instant application in respect of the advantage of the carbonate and carbamate prodrugs, i.e., that their "increased activity can be attributed to increased cellular uptake of the prodrugs followed by intracellular conversion to PMPA, which undergoes subsequent phosphorylation to the antivirally active diphosphate metabolite" (p. 64, lines 11-15).

Barditch-Crovo et al (Exhibit 3)

8.13 Exhibit 3 relates to evaluation of oral prodrug of adefovir (adefovir dipivoxil) for its anti-HIV activity, safety and pharmacokinetics.

Louie et al (Exhibit 4)

8.14 Exhibit 4 relates to assessment of efficacy of tenofovir disproxil fumarate (TDF) monotherapy by following the initial rate of decline in plasma viral load, which is a measure of the efficacy of therapy in blocking viral replication.

9. Discussion on the issue of Section 2(1)(j)

9.1 D1 teaches that the negative charge on the phosphonate group is responsible for limiting the bioavailability of the active compounds possessing such a group. So such nucleotide analog is required to be modified by blocking the negative charges by masking the two hydroxyl groups present in the phosphonate moiety of the parental compounds.

9.2 Page 6 of D1 lists further prodrugs of the basic compounds known wherein L1 is defined as various amidates disclosed therein and L2 (the other protecting group) includes an oxyester.

9.3 The substructure separating the base and the phosphorus moiety in the compounds of the instant application is $-CH_2-OCH(R1)-CH_2-$, which differs from the substructure defined in D1 only by the substitution of an additional group R1.

9.4 The preferred substitutions on the linker group disclosed in D1 (page 25) are compared with the claimed substitutions of the instant application as hereunder:

Claimed substitutions	Disclosed substitutions
Hydrogen	Hydrogen
Methyl	Methyl
CH ₂ OH	CH ₂ OR ₄ , where R ₄ includes H.
CH ₂ F	CH ₂ F
CH=CH ₂	CH=CH ₂
CH ₂ N ₃	CH ₂ N ₃

9.5 Claim 2 of the instant application includes guanin-9-yl, adenin-9-yl, 2,6-diaminopurin-9-yl, 2-diaminopurin-9-yl or their 1-deaza, 3-deaza or 8 aza analogs or cytosin-a-yl. D1 discloses that *preferably, B is a 9-purinyl residue selected from guanyl, 3-deazaguanyl, 1-deazaguanyl, 8-azaguanyl, 7-deazaguanyl, adenyl, 3-deazaadenyl, 1-dezazadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl, or a B is a 1-pyrimidinyl residue selected from cytosinyl, 5-halocytosinyl, and 5-(Ci-C3-alkyl)cytosinyl.*

9.6 D1 discloses at page 9, last paragraph that *some of the compounds of the present invention can exist as optical isomers and both racemic or scalemic and diastereomeric mixtures of these isomers which may exist for certain compounds as well as the individual optical isomers which are all within the scope of the present invention.*

9.7 Therefore, it is evident that the parental compounds disclosed in D1 possess exactly the same structure as the parental compounds of the instant application except the presence of additional optional R1 substitution in the linker group between the heterocyclic base and the phosphorus moiety of the parental compounds.

9.8 The phosphonate protecting groups according to the instant application are $-OC(R_2)O_2C(O)X(R)_a$, an ester, an amidate or $-H$, but at least one Z is $-OC(R_2)O_2C(O)X(R)_a$ such that at least one Z is an oxyester defined above. D1 discloses protecting groups in table 1, page 25.

The protecting group $OC(R_2)O_2C(O)X(R)_a$ is different from the protecting groups of D1 in that "X" according to the instant application is either N or O, which may be optionally substituted whereas D1 discloses carbon atom for X, which may also be optionally substituted.

9.9 According to Grimm, Hydride Displacement Law, 1925 –

‘Atoms anywhere upto four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms in such a manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the groups one to four places respectively to their right’.

Following Grimm’s law, it can be seen that the groups -O-, NH and -CH₂- are classical bioisosters or isosteric equivalents.

9.10 It is therefore obvious for a person having ordinary skill in the art to try structural modifications on the compounds disclosed in D1 on the basis of the interchangeability of these sub-structures (-O-, NH and -CH₂-) and further in view of principle of bioisosterism of D2.

9.11 D3 explains the mechanism of demasking of the prodrugs and teaches that carbamate group is a much preferred protecting group for phosphate and phosphonate containing active agents. Thus, D3 and D4 (which belongs to the same patent family as D3) provides guidelines and motivation to a person having ordinary skill in the art to try structural modifications on the compounds of D1.

9.12 D5 teaches site-specific delivery of the active agents, which are otherwise inaccessible to the preferred site of action. Therefore, D5 teaches a way to increase bioavailability of the modified parental compounds.

9.13 D7 teaches carbonate prodrugs of the parental compound of the instant application.

9.14 Although D5 discloses a mono-protected phosphonate moiety but in light of teachings of D7 and D1 i.e., to protect both the hydroxyl groups of the phosphonate moiety and thus it would have been obvious for a person having ordinary skill in the art to arrive at the bis-protected prodrug.

9.15 D8 discloses that Bis[(pivaloyloxy)methyl] ester of PMEAs displayed an oral bioavailability of 30% and 50% that was 15-fold and 25-fold higher than the bioavailability observed after dosing of PMEAs. As PMEAs is a related compound to PMPA (differing only in the substitution of an additional methyl group at the linker or bridging group), a person having ordinary skill in the art would expect similar prodrugs of PMPA to exhibit at least around 15 to 25% increase in bioavailability upon conversion to similar prodrugs.

Therefore, the bioavailability of the claimed compounds as shown by the applicant’s cannot be considered as unexpected or surprising in view of the "expected" 15 to 25 times increase in bioavailability taught by the disclosure of D8.

9.16 D9 exhibits a 200 fold enhancement in activity of (acyloxy) alkyl phosphonate prodrug of PMEAs. Therefore, the bioactivity of the compounds shown by the applicant cannot be considered as unexpected or surprising in view of the "expected" 200 times increase in bioactivity taught by the disclosure of D9 (PMPA being a closely related compound).

9.17 Decision on the issue

Therefore, without prejudice to my decision in para 5.2.10 regarding non-allowability of the instant application as divisional application, I conclude that the compounds as claimed in claims 1 to 35 are obvious to a person skilled in the art and lack inventive step.

10. Discussion on the issue of Section 3(d)

10.1 Claims 1 to 25, 33 and 34 relates to a compound of formula 1a and formula 1. Claims 26 to 31, 34 and 35 relates to a method of preparing a compound of formula 1a and formula 1.

10.2 The explanation provided in Section 3(d) states that derivatives of known substance shall be considered to be the same substance unless they differ significantly in properties with regard to efficacy. Although there is no standard of how much increase in effect should be considered as ‘unexpected and surprising’, but established principle is it would depend upon the expected increase suggested or motivated by the prior art.

10.3 Pfizer vs Apotex, Decision of the US Court of Appeal for the Federal Circuit, March 22, 2007 –

‘Evidence of unexpected results can be used to rebut a prima facie case of obviousness’

10.4 Quoting In Re Baxter Travenol Labs., 952, F2d, 388, 392 (Fed. Cir. 1991)

‘When unexpected results are used as an evidence of non obviousness, the results must be shown to be unexpected compared with the closest prior art’

10.5 Merck, 874, F2d at 808

‘Thus in order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected’.

10.6 Therefore, the increase in activity shown by the applicant in table 1 and table 2 of the instant application cannot be termed as unexpected or surprising increase compared to the expected increase of above mentioned prior arts. Moreover, no data has been provided to substantiate the enhanced efficacy of the compound claimed in the instant application with respect to their effectiveness in human beings.

10.7 Regarding the exhibits submitted by the applicant in support of efficacy of the claimed compounds, I opine that none of the exhibits supports the same.

Exhibit 1

10.8 The closest prior art to the subject-matter of the instant application is D1. It discloses phosphonates and outlines prodrug synthesis of the same. Thus, at the priority date, a person having ordinary skill in the art was aware from D1 that the modified nucleotide analogs can have improved bioavailability, improved pharmacokinetic or pharmacodynamic properties, enhanced potency and/or improved toxicity characteristics compared to the corresponding unmodified nucleotide analog; from D2 to D9 he is aware

of mechanism of demasking of prodrugs and enhanced activity (200 fold) and bioavailability (30-50%) of esters of PMEA. It was obvious when wanting to obtain prodrugs of PMEA, to combine the teachings of all the above said prior art documents.

10.9 Moreover, the usefulness of transforming drugs into prodrugs in order to solve the type of problems solved in the instant application was already known as early as 1975. It is accepted that no tool was available to reasonably predict success in switching profunctionalites from the (acyloxy) alkyl-type to carbonate or carbamate groups. Yet, the combined teachings of D1 to D9 would lead the skilled person in an obvious manner to make derivatives and testing them would be a matter of routine as shown in D6 and D8 which discloses mechanism of prodrug designing and in vivo evaluation of prodrugs. There is, thus, no inventive activity linked to preparing or testing these compounds.

Exhibit 2 and 3

10.10 Exhibit 2 and 3 relates to the performance of the fumarate salt whereas the instant application pertains to carbamate and carbonate prodrugs of tenofovir, The fumarate salt of tenofovir is not related to inventive concept the instant application

Exhibit 4

10.11 Results of exhibit 4 shows that TDF is a potent antiretroviral agent and its activity is comparable with ritonavir, a potent protease inhibitor i.e.TDF does not show any enhanced activity over the prevailing antiviral drugs.

10.12 Decision on the issue

Therefore, without prejudice to my decision in para 5.2.10 regarding non-allowability of the instant application as divisional application, the claims 1 to 25, 33 and 34 of the instant application are not patentable u/s 3(d) of the Patents (Amendment) Act, 2005 as the applicant failed to show any supporting data to prove that the claimed compounds increased therapeutic efficacy as compared to the closest prior art as discussed above.

11. Discussion on the process claims

11.1 Regarding process claims, section 3(d) says, '....or of the mere use of a known process, machine or apparatus unless such process results in a new product or employs at least one new reactant'.

11.2 The reactants used in the said process claims have been used in D1, D3 and D6 for masking phosphonate group of PMPA. Also as discussed above the formula 1a and 1 lacks inventive step in view of the aforementioned prior art documents.

11.3 Decision on the issue

Therefore, the claims 26 to 31, 34 and 35 are considered as mere use of a known process which results in a known product and not patentable u/s 3(d) of the Patents (Amendment) Act, 2005.

12. Final conclusion and decision

12.1 The instant application cannot be considered as a divisional application u/s 16 and is refused for grant of patent for the reasons as discussed in para 5 of this document.

12.2 After perusing the arguments and evidences of applicant and opponent, I have reached the aforementioned findings. In light of that, it is concluded that the claims 1 to 35 of the instant application lack inventive step and fails to show efficacy. Therefore, the said claims are not patentable u/s 2(1)(j) and 3(d) of the Patents (Amendment) Act, 2005. I hereby refuse the grant of the patent on the instant application.

13. No order for cost.

Date – July 20, 2011

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