**Before the Controller of Patents, New Delhi**

**In the matter of section 25(1) of the Patents Act, 1970;**

**and**

**In the matter of the Patents Rules, 2003**

**and**

**In the matter of patent application no. 2076/DEL/1997, titled "Nucleotide Analogs" by Gilead Sciences, Inc. of 333 Lakeside Drive, Foster City, California, USA (Applicant)**

**and**

**In the matter of representation by way of opposition by [OPPONENT]**

**REPRESENTATION BY WAY OF OPPOSITION UNDER SECTION 25(1) OF THE PATENTS ACT, 1970 AND RULE 55 OF THE PATENTS RULES, 2003 BY [OPPONENTS]**

## I. HEARING REQUESTED

1. The Opponents hereby request a hearing under section 25(1) of the Patents Act (the Act) and Rule 55 of the Patents Rules (the Rules).

## II. DESCRIPTION OF OPPONENT

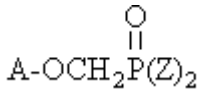
2. 2. The opponents are community based, non-profit organizations representing the needs of people living with HIV/AIDS ("PLHIV"). Sahara Centre for Residential Care and Rehabilitation is a non-profit organisation is registered as society NO. S/15311/1985 under the Societies Registration Act, 1860 in the year 1985 and has its registered office at E-453, Greater Kailash Part-II, New Delhi. Associação Brasileira Interdisciplinar de AIDS ("ABIA") is a private, nonprofit legal entity, constituted and registered in the National Registry of Legally Constituted Entities ((*Cadastro Nacional de Pessoa Jurídica,CNPJ*) under

number 29263068/0001-45, and with headquarters at Avenida Presidente Vargas 446/13º floor, Center, Rio de Janeiro, Brazil.

3. Sahara Centre for Residential Care and Rehabilitation runs a care programme for HIV positive residents and has also opened facility in the nature of a Care Home called 'the Sahara-Michael's Care Home' which provides aupport and care for destitute and terminally ill patients including PLHIV. They provide urgent and specialized medical treatments to PLHIV and they also accommodate and treat them at the above said Care Home. Of particular concern to the Opponents us the impact of the new product patent regime on PLHA's access to safe, effective and affordable HIV/AIDS treatments.
4. ABIA has been acting in the fight against the HIV/AIDS epidemic in Brazil in the areas of prevention, advocacy, social mobilization, adherence to treatment and support for persons living with HIV/AIDS and in the production and dissemination of knowledge and information related to the epidemic and to sexual health for 20 years.
5. One of the most important challenges that the Brazilian AIDS response is facing today is the sustainability of the provision of universal and equitable access to diagnosis, treatment and care services and commodities. Tenofovir is an important antiretroviral drug used to treat HIV, which is now part of the first line treatment for HIV advised by 2007-2008 Brazilian treatment guidelines. Recently the Brazilian health ministry declared tenofovir in the public interest in treating people living with HIV/AIDS in Brazil. However, Brazilian Government will have no source to import tenofovir either as raw material or finished product from Indian generic companies if a patent for the same is granted in India. Therefore, ABIA is concerned about the possible grant on a patent application relating to tenofovir and its adverse impact on the availability of tenofovir in Brazil.

## III. SUMMARY OF THE ALLEGED INVENTION

6. The Application, filed on 25 July 1997 and claiming priority from U.S Application Nos. 08/686,838 and 60/022,708, dated 26 July 1996 (Priority Date), relates to "intermediates for phosphonomethoxy nucleotide analogs, in particular intermediates suitable for use in the efficient oral delivery of such analogs." *Specification* at p. 1, lines 13-15. Specifically, the Application relates to compounds having the following formula (1a):

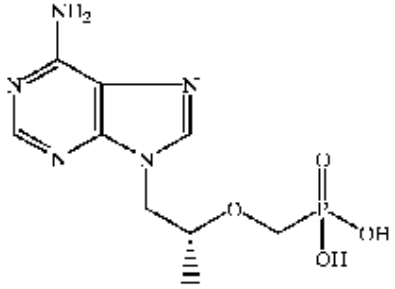


wherein Z is independently $-OC(R^2)_2OC(O)X(R)_a$, an ester, an amidate or -H but at least one Z is $-OC(R^2)_2OC(O)X(R)_a$. *Ibid*. at lines 30-37.

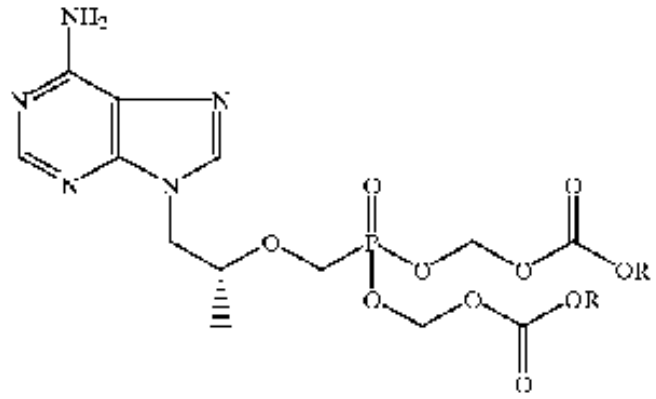
7. Within Z, X can be either nitrogen (thus resulting in a carbamate) or oxygen (thus resulting in a carbonate), and $R^2$ and R are defined as being any number of substituted or unsubstituted hydrocarbons. Further, when X is oxygen, a is 1, and when X is nitrogen, a is either 1 or 2. *Ibid.* at p. 2, lines 2-13.

8. Significantly, everything to the left of Z - that is - $AOCH_2P(O)(OH)_2$, are phosphonomethoxy nucleotide analogs, which the Applicant admits have demonstrated antiviral effects, are well known in the art, ***and are per se not part of the alleged invention***. Indeed, the Applicant admits that such nucleotide analogs have been disclosed in several documents, including US 4,659,825; US 4,724,233; US 5,142,051; US 5,130,427; EP 369,231; EP 494,370; EP 454,427; EP 270,885; EP 269,947; EP 452,935; WO 93/07157; WO 94/03467; and WO 96/23801. *Ibid*. at p. 4, lines 20-29. As the specification goes on to state, this nucleotide analog is typically (*R*)-9-[2-(phosphonomethoxy)propyl]adenine, or PMPA. *Ibid.* at p. 33, line 1.

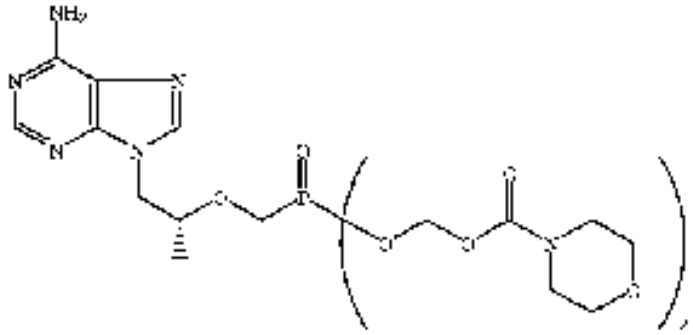
9. Thus, as can be seen in the Examples, PMPA has the following formula:




*Ibid.* at p.49, Example 3. According to the alleged invention, both of the free hydroxyl groups of the phosphonic acid moiety in nucleotide analogs are substituted with "Z," a promoiety that can be a carbonate (i.e., $OC(R^2)_2OC(O)O(R)_a$), a carbamate (i.e., $OC(R^2)_2OC(O)N(R)_a$), an ester, an amidate, or -H, but with at least one Z being a carbonate or a carbamate as defined above. Thus, the resulting prodrugs of the invention include (but are not limited to) the following:



where X is oxygen; *ibid.*, at p. 49, Example 3; or



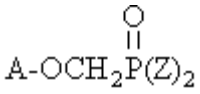
where X is nitrogen. *Ibid*., at p. 54, Example 10.

10. Although the Application claims a much broader class of compounds than carbonates of PMPA, the Specification provides data only on the alleged improvement in the oral bioavailability and antiviral activity of only a limited subset of PMPA ***carbonates*** over PMPA. *Ibid.*, pp. 56-65, Examples 15, 16. Significantly, however, the Applicant does not provide such comparable data on such alleged improvements for PMPA ***carbamates*** over PMPA, ***nor does it provide any data on the alleged improvement of carbonates or carbamates of any of the other nucleotide analogs that are covered by the claims***.

## IV. SUMMARY OF CLAIMS

11. The claims of the Application, as amended, can be summarized as follows:

Claim 1 claims a compound having formula (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 $-OC(R^2)_2OC(O)X(R)_a$;

$R^2$ 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 unsbustituted or is substituted with 1 or 2 halo, cyano, azido, nitro or $-OR^3$ in which $R^3$ is $C_2$-$C_{12}$ alkyl, $C_2$-$C_{12}$ alkenyl, $C_2$-$C_{12}$ alkyyl or $C_5$-$C_{12}$ aryl;

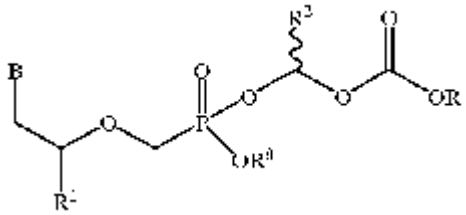
R is independently -H, $C_1$-$C_{12}$ alkyl, $C_5$-$C_{12}$ aryl, $C_2$-$C_{12}$ alkenyl, $C_2$-$C_{12}$ alkynyl, $C_7$-$C_{12}$ alkenylaryl, $C_7$-$C_{12}$ alkynylaryl, or $C_6$-$C_{12}$ alkaryl, any one of which is unsbustituted or is substituted with 1 or 2 halo, cyano, azido, nitro, $-N(R^4)_2$ or $-OR^3$ where which $R^4$ independently is -H or $C_1$-$C_8$ 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 $-O R^3$ or (c) both N-linked R groups can be -H;

and the salts, hydrates, tautomers and solvates thereof.

12. Claim 2 is dependent on claim 1, and claims compounds of the following formula (1):




wherein B is guanine-9-yl, adenine-9-yl, 2,6-diaminopurin-9-yl, 2-aminopurin-9-yl or their 1-deaza, 3-deaza, or 8-aza analogs, or B is cytosine-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

unsbustituted or is substituted with 1 or 2 halo, cyano, azido, nitro or -$OR^3$ in which $R^3$ is $C_2$-$C_{12}$ alkyl, $C_2$-$C_{12}$ alkenyl, $C_2$-$C_{12}$ alkyyl 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 -$CH_2$-;

$R^2$ is independently hydrogen or $C_1$-$C_6$ alkyl; and

$R^8$ is hydrogen or -$CHR_2$-O-C(O)-OR, or $R^8$ is joined with $R^1$ to form -$CH_2$-;

and the salts, hydrates, tautomers and solvates thereof.

13. Claims 3-18 are dependent claims that narrow the scope of the compounds covered in claims 1 and 2.

14. Claims 19 covers the method for preparing a compound of formula (1a) comprising reacting the diacid of the phosphonomethoxy nucleotide analog with L-CH($R^2$)OC(O)X(R)n wherein L is a leaving group to obtain a compound of formula (1a) as described above.

15. Claims 20-22 are dependent to claim 19, and cover methods of preparing compounds of formulae (1a) and (1) under specific conditions.

16. Claims 23-24 are omnibus claims, and claim the compounds and methods for preparing the compounds of formula (1a) as described in the specification.

## V. GROUNDS OF OPPOSTION

17. The Opponent bases its representation by way of opposition on the following grounds:

- All of the claims fail to satisfy the inventive step requirement of section 2(1)(ja) of the Act, and is thus not an invention under section 2(1)(j) of the Act. As such, the Opponent brings this representation by way of opposition under section 25(1)(e) of the Act.

- Claims 1-18 and 23 are not inventions under section 3(d) of the Act, as they cover new forms of a known substance which does not result in the significant enhancement of the known efficacy of the substance. As such,

the Opponent brings this representation by way of opposition under section 25(1)(f) of the Act.

18. Furthermore, the Opponent requests that the Controller exercise its powers under section 8(2) of the Act and Rule 12(3) of the Rules to require the Applicant to furnish information relating to objections in respect of patentability that have arisen to the same or substantially the same invention in other jurisdictions, specifically, with respect to the recent non-final rejection, by the United States Patent and Trademark Office upon a request for re-examination, of the equivalent United States patent.

## VI. LEGAL ANALYSIS OF THE CLAIMS

### A. Summary of the Background Literature

#### 1. The concept of developing prodrugs for nucleotide analogs was known in the art.

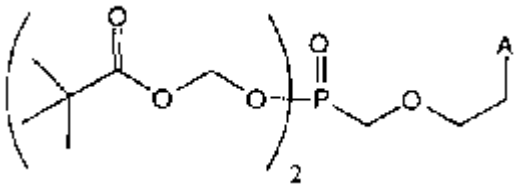
19. As mentioned, the alleged invention described in the Application relates to the use of carbonate/carbamate promoieties in substituting the free hydroxyl groups of the phosphonic acid moiety of a class of known phosphonomethoxy nucleotide analogs. However, the need to create suitable prodrugs for phosphate and phosphonate compounds were well known for decades prior to the alleged invention, as the negatively charged phosphorous in these compounds resulted in their having low cellular permeability and low oral bioavailability. *See* e.g., Liebman, et al, J. Biol. Chem 216:823-830 (1955).

20. Specifically with respect to nucleotide analogs, the need for developing appropriate prodrugs was well known. Although nucleotide analogs, including those encompassed by the present Application, were known to have potential use as antiviral agents, the presence of the negative charges on the phosphorous limited their utility. Indeed, in 1995, Jones and Bischofberger, in "Minireview: nucleotide prodrugs," *Antiviral Research*, 27:1-17 (1995) (attached hereto as

**Exhibit A**), undertook a limited review of the literature relating to prodrugs for nucleotide analogs, and observed thus:

> The area of nucleotide analogs has received a lot of attention recently due to the discovery of nucleotides with potent antiviral activities. Since the negative charge(s) on the phosphorous entail(s) nucleotides with short comings (low permeability and bioavailability), increasing work in the literature is focusing on overcoming these difficulties with nucleotide prodrugs, an approach which temporarily masks the negative charges and liberates the parent nucleotide at a specific site. Exhibit A at p. 2.

21. Specifically, Jones disclosed a prodrug of PMEA having the following formula:




Jones, Exhibit A, at p. 3. As is evident from comparing the above formula to the compounds disclosed in the present Application, the structure of the parental compounds are very similar. More importantly, the acyloxyalkyl promoiety disclosed above: $-OCH_2OC(O)C(CH_3)_3$ - bears close similarities with Z in the present Application, which is defined as $-OC(R^2)_2OC(O)X(R)_a$.

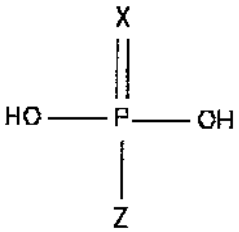
22. Indeed, the specification states that "in most embodiments R2 is H in both instances. *Specification* at p. 5, lines 9-10; *see also* claims 3 and 5. Moreover, R is defined, *inter alia*, as C1-C12 alkyl. Thus, in the only critical difference between the promoiety disclosed above and that being claimed in the present Application is that the carbon is substituted with either oxygen or nitrogen, thus resulting in a carbonate or carbamate, rather than the unsubstituted acyloxymethyl promoieties as disclosed in Jones.

**2. The concept of developing prodrugs for a wide range of phosphorous-bearing drugs in general was well known in the art.**

23. Moreover, the desirability of creating suitable prodrugs to mask the negative charge of the phosphorous was not limited to nucleotide analogs. Indeed, this was known to be a common problem that was shared by a wide range of phosphorous containing drugs. For instance, WO91/19721 (the '721 patent), entitled "Phosphorous Prodrugs," (published on 26 December 1991, attached hereto as **Exhibit B**), described the problem thus:

> Phosphate derivatives are key metabolic intermediates in virtually all aspects of cellular metabolism. In addition many antineoplastic and antiviral drugs require intracellular phosphorylation in order to be biologically active. However, the pharmacological utility of phosphate derivatives is severely hampered by the inability of negatively charged phosphate derivatives to permeate into cells and through the blood brain barrier. In addition phosphate and phosphonate compounds in general have a very low oral bioavailability. '721 Patent, Exhibit B at p. 1.

24. In order to overcome these well-known problems of phosphorous-bearing drugs, the '721 patent sought to provide prodrugs that would convert one or more of the hydroxy groups on the phosphorous into a phosphate ester. Thus, the strategy of converting a phosphorous bearing drug with the generic formula:




where X could be either oxygen or sulphur, and Z defined by the structure of the parent drug, was disclosed. *Ibid.* at pp. 4-8.

25. Although the specific promoiety that is disclosed in the '721 patent differs from the carbonate/carbamate promoieties that are being claimed in the present Application, it is evident from the disclosures contained in the '721 patent that the problems generally facing all phosphorous bearing drugs (i.e., poor intracellular permeability, low oral bioavailabililty) were known well before the Priority Date, as was the general strategy of overcoming this problem by substituting the hydroxy groups with a suitable promoiety.

26. Thus, a person skilled in the relevant art would have been well-acquainted with not only the background literature relating to prodrugs for nucleotide analogs, but with prodrugs generally, and especially with that relating to prodrugs for phosphorous-bearing drugs. Therefore, a person skilled in the art who was searching for an appropriate promoiety for the specific class of nucleotide analogs that are covered in the present Application would readily have been able to recognize that the teachings from prior art references that disclosed prodrugs for other phosphorous bearing drugs could potentially be applicable to the task at hand.

**B. The Applicant's Admissions Limit the Scope of the Alleged Invention**

27. As admitted by the Applicant, the nucleotide analog compounds of the structure $AOCH_2P(O)(OH)_2$ have demonstrated antiviral activity, ***are well known in the art and are per se not a part of the alleged invention***. *Specification*, at p. 4, lines 20-30. By extension, "B" and "$R^1$" in formula (1) of claim 2, which themselves form part of the known class of nucleotide analog compounds, must also *per se* not be part of the alleged invention. Therefore, no matter what B or $R^1$ are defined as in the claims, by the Applicant's own admissions, they are merely part of the known class of nucleotide analog compounds and *per se* do not form part of the invention.

28. The only aspect of the alleged invention, as per the Applicant's own admissions, that is allegedly not known in the art is the promoiety "Z," which substitutes the hydroxy groups of the phosphonic acid moiety of the known nucleotide analog

compounds, and where one or both is a carbonate or carbamate, depending on whether X is oxygen or nitrogen.

29. Thus, the Opponent submits that if it can show that it would have been obvious to a person skilled in the art to utilize Z as a promoiety to substitute the hydroxy groups on the phosphonic acid moiety for any one of the instances of known nucleotide analogs, it would, by extension, have been obvious to utilize Z for ***any*** of the known nucleotide analogs, ***no matter how B or $R^1$ are defined in the claims,*** as they do not form part of the invention, according to the Applicant's own admissions. Thus, claims 2, 4, 6, 11, 13-15, and 17-18, which are dependent claims that merely narrow the definition of either B or $R^1$, need not be dealt with separately, and fail insofar as claim 1, or any of the other claims upon which they are dependant, fail.

### C. The Product Claims 1-18 and 23 (as Amended) Fail for Lack of Inventive Step Under Section 2(1)(ja) of the Act.

30. The Opponent submits that claims 1-18 and 23 would have been obvious to a person skilled in the art, and thus fail for lack of inventive step as defined in section 2(1)(ja) of the Act. Under section 2(1)(j) of the Act, an invention is defined as "a new product or process involving an inventive step and capable of industrial application." Section 2(1)(ja) in turn defines "inventive step" as "a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art." As substituting the hydroxyl groups on the phosphorous with the carbonate/carbamate promoieties being claimed in the instant Application would have been obvious to a person skilled in the art, claim 1, and all of its dependent product claims fail for lack of inventive step.

#### 1. The carbonate/carbamate promoieties as claimed in the Application were known in the art.

31. As mentioned, the nucleotide analogs that are encompassed in the Application are *per se* not part of the alleged invention. Thus, the only allegedly "novel" and

"inventive" aspect of the alleged invention is the substitution of both hydroxyl groups with Z, which is defined as independently $-OC(R^2)_2OC(O)X(R)_a$, an ester, an amidate or -H but with at least one Z being $-OC(R^2)_2OC(O)X(R)_a$.

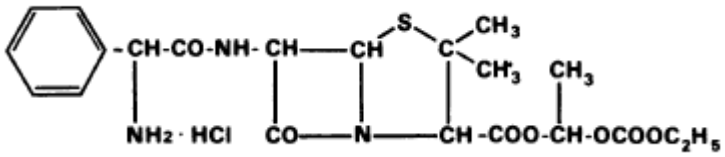
32. As the review of the background literature above demonstrates, the strategy of converting nucleotide analogs into suitable prodrugs by masking the hydroxyl groups on the phosphonic acid moiety was well known before the Priority Date. Moreover, the strategy of developing suitable prodrugs to mask the negative charge of the phosphorous was well known, not just with respect to nucleotide analogs, but across a wide array of drugs.

33. Thus, for a person skilled in the art faced with the task of finding a suitable promoiety for use with the nucleotide analogs encompassed by the present Application, it would have been readily apparent to him/her to conduct an investigation into the promoieties that had been disclosed in the literature in order to determine which was the most appropriate in this particular case. As will be demonstrated below, carbonate/carbamate promoieties that are essentially identical to those being claimed in the present Application were well-known in the art. Further, due in part to their close structural similarity to the unsubstituted acyloxyalkyl promoieties as disclosed in Jones (and discussed above), it would have been obvious to a person skilled in the art to utilize such carbonate/carbamate promoieties to convert the nucleotide analogs at issue into suitable prodrugs.

34. Indeed, as far back as 1975, carbonate promoieties essentially identical to that being claimed in the instant Application were known in the art and successfully utilized to improve the absorption characteristics of poorly bioavailable drugs. In that year, Bodin, et al, *Bacampicillin: a New Orally Well-Absorbed Derivative of Ampicillin*, Antimicrobial Agents and Chemotherapy, Vol. 8, 5:518-525 (1975) (attached hereto as **Exhibit C**) described a new oral prodrug of the antibiotic ampicillin. After describing the problems caused by low absorption levels of ampicillin, they stated:

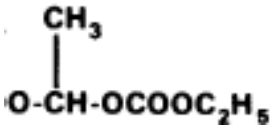
> Certain esters of ampicillin, namely, ***pivampicillin*** and talampicillin, have been found to be well absorbed when given orally and undergo hydrolysis in the body to give peak levels of ampicillin higher than those obtained with ampicillin itself. ***These esters are analogues of acyloxyalkyl esters***…We now describe a new type of hydrolyzable ester group ***containing a carbonate moiety with which it is possible to improve the oral absorption*** of ampicillin and other types of ß-lactam antibiotics.

Bodin, et al, Exhibit C, at p. 518 (emphasis added). The authors thus described a carbonate prodrug of ampicillin of the following formula:



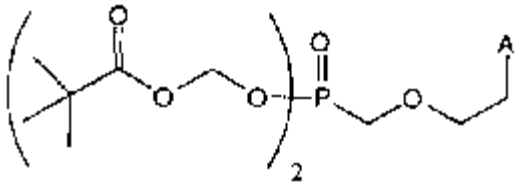

*Ibid.* at p. 519.

35. As is evident from the above, the carbonate promoiety that is attached to the ampicillin moiety, i.e.:

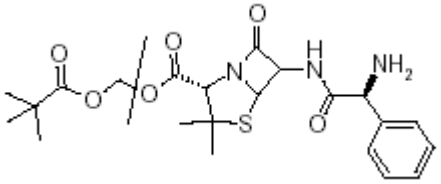



can be represented as $-OC(R)_2OC(O)OR'$, which is identical to "Z" when X is O. Moreover, as the authors make clear, their motivation to create this particular carbonate promoiety was based upon the past successes in creating pivampicillin and other acyloxyalkyl esters for ampicillin. *Ibid*. at p. 518.

36. It is important here to observe that the acyloxyalkyl promoiety utilized in pivampicillin is identical to the promoiety used for PMEA as disclosed in Jones. Compare PMEA dipivoxil:



with pivampicillin:

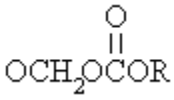


37. Thus, not only were carbonate promoieties essentially identical to "Z" well known in the art for nearly 20 years prior to the present application, it was established that the successful use of an acyloxyalkyl promoiety for a given drug would give a person skilled in the art motivation to try, and a reasonable expectation of success in utilizing, a similar carbonate promoiety for that drug or a close structural analogue. As such, it would have been obvious to one skilled in the art, given the successes in creating PMEA dipivoxil, to utilise a carbonate promoiety for PMPA.

38. As will be further demonstrated below, other prior art references disclosed the use of both carbonate/carbamate promoieties essentially identical to "Z" in creating suitable prodrugs for phosphorous-bearing drugs.

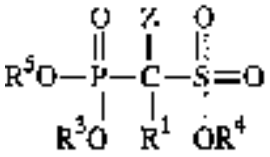
**2. The carbonate promoieties as claimed in the Application were known in the art for use in phosphorous-bearing drugs.**

39. According to the specification, when X is oxygen, the resulting carbonate promoiety will, in most embodiments, have the formula:



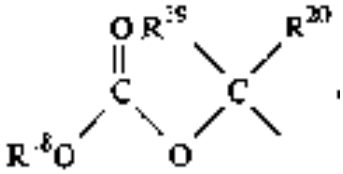
40. However, US 5,470,845 (the '845 patent) (published 28 November 1995, attached hereto as **Exhibit D**), discloses a promoiety that is essentially identical to the

above. The '845 patent, like the present Application, discloses a series of suitable "prodrug esters" for phosphorous-bearing drugs having the structural formula:

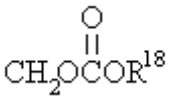


wherein $R^3$ and $R^5$ are defined as "prodrug esters." '845 Patent, Exhibit D at columns 4-6. As is evident from the above formula, the "prodrug esters" substitute both hydroxyl groups on the phosphorous, precisely as "Z" substitutes both hydroxyl groups of the phosphorous in the present Application.

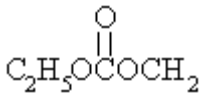
41. The '845 patent further goes on to state that "the term "prodrug esters" as employed ***herein includes prodrug esters which are known in the art for both phosphorous*** and carboxylic acids." *Ibid.* at column 6, lines 13-16. The '845 patent goes on to show an example of such known prodrug esters, such as:



Wherein $R^{18}$, $R^{19}$ and $R^{20}$ are H, alkyl, aryl or arylalkyl; ***however $R^{18}O$ cannot be HO***." *Ibid*. at column 6, lines 16-23 (emphasis added). Thus, where $R^{19}$ and $R^{20}$ are both H, we are left with a carbonate promoiety of the following:



where $R^{18}$ is an alkyl, aryl or arylalkyl. As is evident, this carbamate promoiety, which substitutes both hydroxyl groups on the phosphorous-bearing drug (represented in the '845 patent as "$OR^3$ and $OR^5$") is essentially identical to the carbonate promoiety described in the present Application. Indeed, the '845 patent specifically lists as an example the following carbonate as a suitable prodrug ester:



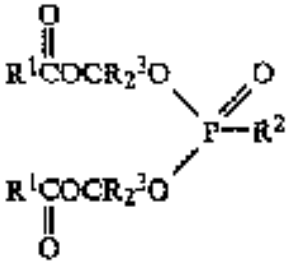
*Ibid.* at column 6, lines 32-34.

42. Thus, as the foregoing demonstrates, carbonate promoieties essentially identical to those being claimed in the instant Application were "known in the art for both phosphorous and carboxylic acids," *Ibid.* at column 6, lines 13-16, and were disclosed in the '845 patent as suitable for substituting the free hydroxyl groups on a phosphorous-bearing drug. As such, it would have been readily apparent and obvious to a person skilled in the art to examine these carbonate promoieties in developing a suitable prodrug for the nucleotide analogs in the present Application. This is particularly true given the established similarities between the carbonate promoiety that is disclosed in the '845 patent and the unsubstituted acyloxymethyl promoieties as disclosed in Jones, as discussed above. As such, to the extent that the claims in the Application cover a carbonate promoiety that was already disclosed in the '845 patent, they fail for lack of inventive step.

**3. The carbamate promoieties as claimed in the Application were also known in the art for use in phosphorous-bearing drugs.**

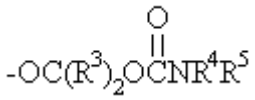
43. As mentioned, Z can be either a carbonate or a carbamate depending on whether X is oxygen or nitrogen. As has already been demonstrated, the use of carbonate promoieties in the development of suitable prodrugs for phosphorous-bearing drugs was well known in the art, and was obvious to a person skilled in the art. Likewise, carbamate promoieties that are essentially identical to those claimed in the Application were well known in the art.

44. US Patent 4,816,570, (the '570 patent) entitled "Biologically Reversible Phosphate and Phosphonate Protective Groups," (published 28 March 1989, attached hereto as **Exhibit E**) discloses a series of protective groups which are suitable for masking phosphates and phosphonates with the following formula:



Wherein $R^3$ is hydrogen or alkyl hydrocarbon, preferably hydrogen or methyl group, and $R^2$ is "***part of the parent phosphate or phosphonate***," and "***can be any organic or inorganic residue***." *Exhibit E*, column 3 at lines 33-37 (emphasis added). Finally, $R^1$ is defined as "hydrogen; alkyl; alkaryl, or aryl hydrocarbon, or an organic derivative thereof; or ***amine***. $R^1$ is preferably an alkyl, alkaryl, or aryl hydrocarbon having from 1-10 carbon atoms; ***or an amine having the formula $NR^4R^5$***, where $R^4$ and $R^5$ are independently hydrogen or an alkyl hydrocarbon having from 1-10 carbon atoms. $R^1$ is most preferably an alkyl, alkaryl, or aryl hydrocarbon having from 1-6 carbon atoms; ***or $N(CH_3)_2$***." *Ibid*. at line 15-40 (emphasis added).

45. Thus, as the foregoing makes clear, the '570 patent discloses carbamate promoieties of the general formula:



where $R^3$ is hydrogen or alkyl hydrocarbon, and $R^4R^5$ are independently hydrogen or an alkyl hydrocarbon having from 1-10 carbon atoms. As is evident, this carbamate promoiety is substantially identical to the carbamate promoiety that is being claimed in the present Application. Moreover, the '845 patent specifically states that $R^2$, or the residue of the parent drug, can be "any organic or inorganic residue," and the method described "***has potential applications in…developing new anticancer, antiviral and antiparasitic drugs***." *Ibid*. column 3, lines 35-36; column 4, lines 23-27 (emphasis added).

46. Thus, the '845 patent discloses a carbamate promoiety substantially identical to that claimed in the instant Application, and is specifically directed to providing

appropriate prodrugs for phosphate and phosphonate compounds, with the expectation that such methods can be applied in developing new antiviral drugs. As such, a person skilled in the art would have interpreted the disclosures of the '845 patent as an unmistakable direction to apply its teachings in deriving suitable prodrugs for any number of phosphorous-bearing compounds, including the nucleotide analogs that are encompassed in the present Application. Therefore, the claims in the present Application, to the extent that they cover carbamate promoieties substantially identical to those disclosed in the '845 patent, fail for lack of inventive step.

**4. The close structural similarities between the promoieties disclosed in Jones and the promoieties claimed in the present Application render the alleged invention obvious.**

47. As demonstrated above, the carbonate and carbamate promoieties claimed in the present Application were known in the art and were known to be useful in masking the negative charge of phosphorous-bearing drugs. Further, as the disclosures in Jones make clear, promoieties of the formula $OCH_2OC(O)CH(CH_3)_3$ were known to be effective in creating a prodrug of a nucleotide analog bearing a close structural similarity with the nucleotide analogs of the present Application. Jones, Exhibit A at p. 3. As observed above, the only essential difference between the promoiety disclosed in Jones and the carbonate/carbamate promoieties claimed in the present Application is the substitution of the carbon with X, which can either be oxygen or nitrogen.

48. The Opponent submits that due to the close structural similarity between the unsubstituted acyloxyalkyl promoiety disclosed in Jones to the carbonate and carbamate promoieties that were already known in the art and which are now being claimed in the present Application, it would have been obvious to a person skilled in the art to try to obtain a suitable promoiety by substituting the methylene group with its classic bioisosteres, O and NH to obtain the corresponding carbonate and carbamate promoieties. This is particularly true where the prior art demonstrated that the successful use of an acyloxyalkyl

promoiety on a given drug (such as ampicillin) would motivate a person skilled in the art to also utilise the corresponding carbonate promoieties on the same or similar drug with a reasonable expectation of success. See Bodin, et al., Exhibit C at p. 518.

49. The fact that the carbonate and carbamate moieties were not specifically disclosed in the prior art references as useful for *nucleotide prodrugs* in particular need not, and should not, obviate the finding of obviousness. The Supreme Court of the United States, which has liberal standards on patentability as compared to India, as part of an increasingly global recognition that "granting patent protection to advances that would occur in the ordinary course without real innovation retards progress," recently held, in a landmark judgment:

> Common sense teaches…that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle…A person of ordinary skill is also a person of ordinary creativity, not an automaton.
>
> The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." ***When there is a design need or market pressure to solve a problem and there are a finite number of identified predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.***

*KSR Int'l Co. v Teleflex, Inc.*, 550 U.S. __ (2007), slip opinion at pp. 15, 16-17 (attached hereto as **Exhibit F**) (emphasis added).

50. Here, as in the *KSR* case, there was a well-established "market pressure" to solve the problem of obtaining a suitable prodrug of the known nucleotide analogs described in the Application. Moreover, there were a "finite number of identified

predictable solutions" - i.e., acyloxyalkyl promoieties and their known bioisosteric carbonate/carbamate derivatives - which would result in the "anticipated success" of increased oral bioavailability and enhanced cellular absorption. As such, the Opponents submit that the resulting products, as claimed in the present Application, were a result not of "innovation" but of "ordinary skill and common sense."

51. Therefore, the Opponents request that claim 1, and its dependent claims 2-18 and 23 (as amended), be denied as failing to satisfy the inventive step requirement of section 2(1)(ja) of the Act.

**D. The Method Claims 19-22 and 24 (as Amended) Fail for Lack of Inventive Step Under Section 2(1)(ja) of the Act.**

52. Claim 19 (as amended) claims the "method for preparing antiviral phosphonomethoxy nucleotide analogue prodrug of formula (1a) comprising reacting in a manner hereinbefore described the diacid of a phosphonomethoxy nucleotide analog along with L-CH(R2)OC(O)X(R)a wherein L is a leaving group to obtain a compound of formula (1a)."

53. The phosphonomethoxy nucleotide analogues are admitted to be known in the art by the Applicant. Moreover, as has been established above, the promoiety, CH(R2)OC(O)X(R)a, was known in the art, and the use of such a promoiety in developing a suitable nucleotide analog prodrug as described in formula (1a) was obvious to a person skilled in the art. Finally, the method of preparing a compound of formula (1a) by using L as a leaving group has been admitted by the Applicant as obvious to a person skilled in the art:

> The carbamates and carbonates of this invention are prepared from the diacids of the phosphonomethoxy nucleotide analogues and the synthon LCH(R2)OC(O)X(R)a. L is a leaving group such as Cl, ***although it will be appreciated that any of the conventional leaving groups used in organic chemistry in nucleophilic substitution reactions can be successfully employed in place of chloro…***The carbamates are prepared by reacting the synthon with

> the nucleotide analogs ***under typical conditions of nucleophilic attack…***The carbonates are formed by reacting the appropriate synthon with the nucleotide analog in the presence of an ***organic base, typically amine base***. Specification, at p.32-33.

54. As the foregoing makes clear, insofar as the aim of deriving a nucleotide prodrug of the formula (1a) with the carbonate/carbamate promoiety is obvious, the method for preparing such a compound will be readily obvious to a person skilled in the art, as they merely involve well known methods used in organic chemistry in nucleophilic substitution reactions. Thus, claim 19, and its dependent claims 20-22 and 24 (as amended), which merely specify the general conditions under which such nucleophilic substitution reactions take place, fail for lack of inventive step because the product claims fail for lack of inventive step.

**E. Product Claims 1-18 and 23 (as Amended) Are Not Inventions within the Meaning of the Act Because they Are New Forms of Known Substances without a Significant Enhancement in Known Efficacy.**

55. Without prejudice to and in the alternative to the foregoing, the Opponent submits that claims 1-18 and 23 (as amended) are not inventions under section 3(d) of the Act. The product claims 1-18 and 23 (as amended) all relate to a new form of a known substance - i.e., ester prodrugs of the known class of nucleotide analogs. Under section 3(d) of the Act, "the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance" is not an invention within the meaning of the Act. The Explanation to section 3(d) provides, "For the purposes of this clause, salts, ***esters***….and other derivatives of known substance shall be considered to be the same substance, ***unless they differ significantly in properties with regard to efficacy***," (emphasis added). From the clear meaning of the Explanation, the compounds described in the Application fall under section 3(d) of the Act.

56. In a recent judgment upholding the validity of section 3(d) against a Constitutional challenge, the Madras High Court had occasion to expound on the

meaning of section 3(d) as it relates to new forms of known substances at some length:

> The position therefore is, if the discovery of a new form of a known substance must be treated as an invention, ***then the patent applicant should show that the substance so discovered has a better therapeutic effect.*** Darland's Medical Dictionary defines the expression "efficacy" in the filed of pharmacology as "the ability of a drug to produce the desired therapeutic effect" and ***"efficacy" is independent of the potency of the drug***….In other words, the patent applicant is definitely aware as to what is the "therapeutic effect" of the [known substance] and what is the difference between the therapeutic effect of the [known substance] and the drug in respect of which patent is asked for. ***Therefore it is a simple exercise…for any patent applicant to place on record what is the therapeutic effect/efficacy of a known substance and what is the enhancement in that known efficacy***."

*Novartis AG and Another v. Union of India and Others*, (2007) 4 MLJ 1153 (attached hereto as **Exhibit G**).

57. As the foregoing demonstrates, the Madras High Court's judgment lays down several axioms that are relevant to the present Application: (1) It is the Applicant's burden to show a significant enhancement in efficacy; (2) "Efficacy" as used in section 3(d) means the ability of the drug to produce the desired therapeutic effect and is independent of the "potency of the drug;" and (3) the Applicant must "place on record" evidence relating to both the therapeutic effect of the known substance *and* evidence relating to the alleged enhancement of efficacy.

58. The Applicant has, to varying degrees, failed to satisfy all three of the above requirements under section 3(d) of the Act. The only evidence that the Applicant has provided in the specification that could be considered to be evidence of enhanced efficacy are contained in Examples 15 and 16 of the Specification,

which purport to determine the oral bioavailability of a series of PMPA carbonates in beagle dogs, and compare the antiviral activity of PMPA carbonates as against PMPA. *Specification,* at pp. 56-65.

59. However, the Applicant has only provided data pertaining to only a small subset of the many possible permutations of PMPA carbonates that are being claimed. With respect to the alleged enhancement in bioavailability, Table 1 of the Specification provides data only relating to eleven possible permutations of PMPA carbonate. *Ibid.* at pp. 61-63. With respect to the alleged enhancement in antiviral activity Table 2 of the Specification provides evidence relating to only six possible permutations of PMPA carbonate. *Ibid*. at p. 65.

60. However, depending on what R, $R^2$ $R^3$ and $R^4$ are, there are quite literally hundreds of possible permutations of PMPA carbonate, as illustrated by the 13-page recitation of the possible permutations as listed in Table B of the Specification. *Ibid.* at pp. 10-22.

61. Moreover, the Applicant has ***failed to provide any data*** relating to the alleged bioavailability and antiviral activity of PMPA ***carbamates***. Similarly, the Application has provided no data relating to either the carbonate or carbamate of any of the other nucleotide analogs other than PMPA that are encompassed by the claims. Thus, as a matter of law, the Applicant has failed to discharge its burden under section 3(d) of the Act to present evidence upon which one can conclude that all of the possible permutations of the prodrugs described in the Application result in a significant enhancement of efficacy.

62. Accordingly, the Opponent submits that, as a preliminary matter, all permutations for which the Applicant has provided no data relating to efficacy be denied, as the Controller is left with insufficient information to make an appropriate determination of efficacy as required under section 3(d).

63. Secondly, as the Madras High Court has made clear, it is the Applicant's burden to “place on record” evidence relating not only to the alleged enhancement of efficacy of the substance being claimed, but the “therapeutic effect/efficacy” of the known substance as well. *Novartis*, Exhibit G at para 13. Thus, for the

Controller to make a determination that there was an "enhancement in known efficacy" as required under section 3(d) of the Act, the Controller must be presented with data that shows the baseline from which the alleged enhancement is being measured.

64. However, as is evident from the data showing the alleged increase in bioavailability, the Applicant has failed to "place on record" data relating to the bioavailability of unmodified PMPA. *Specification*, Table 1 at pp. 61-63. Although Table 1 contains (incomplete) data relating to the pharmacokinetic profile of eleven PMPA carbonates, ***there is no data relating to the pharmacokinetic profile of PMPA***. Thus, even assuming, without admitting, that a demonstrable and significant enhancement in bioavailability can be equated with an enhancement in known efficacy, the Applicant has failed to "place on record" sufficient data with which the Controller can make this determination.

65. Accordingly, the Opponent submits that for all of the possible permutations of PMPA carbonates for which the Applicant has failed in its burden to place on record data relating to the known substance, they fail under section 3(d) of the Act.

66. Finally, the Madras High Court made a sharp distinction between the *potency* of a given drug, and its "*therapeutic efficacy*." Potency of a drug relates to the ***quantum*** of a drug necessary to produce a particular effect, whereas "therapeutic efficacy," as the Court explained, is "the ***ability*** of a drug to produce the desired therapeutic effect." *Novartis*, Exhibit G at para 13. The clear implication of the Court's distinction between "potency" and "therapeutic efficacy" was that evidence of the former is insufficient to meet the requirements of section 3(d) - that is, a showing of an enhancement of the known *potency*, without more, does not satisfy the enhanced efficacy requirement.

67. The Applicant, in Example 16 of the Specification, only provides data relating to the alleged enhancement in *potency* of the PMPA carbonates over unmodified PMPA. As the Applicant states, "The carbonate prodrugs exhibited increased ***potency*** compared to PMPA." *Specification* at p. 64. Indeed, the parameters

utilized in Example 16 only measured the ***concentration*** of the drug necessary to inhibit and kill 50% of the cells. This is a measure of potency, and not pf therapeutic efficacy, and is thus insufficient to meet the enhanced efficacy requirement as expounded upon by the Madras High Court. As such, the six remaining permutations of PMPA carbonates, as described in Example 16 also fail under section 3(d).

68. In summary, all of the product claims, 1-18 and 23 (as amended) fail under section 3(d) of the Act because the Applicant has failed to demonstrate that these new forms result in the enhancement of the known efficacy. First, the Applicant has failed to provide any data relating to the efficacy of the vast majority of the compounds claimed in the Application, including many PMPA carbonates, all PMPA carbamates, and all carbonate/carbamates of the other nucleotide analogs covered by the claims. Second, the Applicant has failed in its burden to place on record any data relating to the known pharmacokinetic profile of unmodified PMPA with which to use as a baseline against the data provided in Table 1. Finally, the data relating to six PMPA carbonates provided in Table 2 relate, at best, to the enhanced *potency* of PMPA carbonates over PMPA, and thus are insufficient to show enhanced efficacy. Therefore, all of the product claims must fail under section 3(d) of the Act.

## VIII. CONCLUSION

69. Given all of the foregoing, the Opponents humbly pray:

(i) For an order refusing all claims (as amended) for lack of inventive step under section 2(1)(ja) of the Act;

(ii) For an order refusing claims 1-18 and 23 (as amended) as they are not inventions within the meaning of the Act under section 3(d);

(iii) For an order refusing any requests by Applicant for leave to amend its Application;

(iv) For a copy of any reply statement and evidence and / or amended specifications that may be filed by the Applicant and a further opportunity to file a rejoinder and rebut the same;

(v) For leave to amend the opposition, as and when required, in light of the amended specifications;

(vi) For a hearing under section 25(1) of the Act read with rule 55(1) of the Patents Rules;

(vii) For costs;

(viii) For such further and other orders as may become necessary in the circumstances of the case.

**Respectfully Submitted,**

On Behalf of Sahara Centre for Residential Care and Rehabilitation,

On Behalf of *Associação Brasileira Interdisciplinar de AIDS* (ABIA),

Place:

Date: