

# **The Patents Act, 1970**

## **IN THE MATTER OF:**

**A representation under s25(1) of The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005 (“the Act”) and Rule 55 of The Patents Rules, 2003 as amended by the Patents Rules, 2006 (“the Rules”) by the Indian Network for People Living With HIV/AIDS (“INP+”) and the Delhi Network of Positive People (“DNP+”) (“the OPPONENTS”)**

**And**

## **IN THE MATTER OF:**

**Indian Application No. 2076/DEL/1997 A in the name of GILEAD SCIENCES, INC. (“the APPLICANT”)**

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### **STATEMENT OF CASE OF THE OPPONENTS**

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1. The Opponents are community based, non-profit organisations representing the needs of people living with HIV/AIDS (“PLHAs”). The Indian Network for People Living With HIV/AIDS (“INP+”) is registered as Society No. 231/1997 under the Tamil Nadu Societies Registration Act 1975, having its registered address at Flat No.6, Kash Towers, 93 South West Baag Road, T.Nagar, Chennai, 600 017. The Delhi Network of Positive People (“DNP+”) is registered as Society No. S-52850 under the Societies Registration Act XXI 1860, having its registered address at House No. 136, Village Neb Sarai, New Delhi, 110068.

2. The Opponents represent and provide support for PLHAs at the local, regional and national levels in order to facilitate systemic change in critical areas such as care and support, access to treatments and addressing issues of discrimination facing PLHAs in Indian society. Of particular concern to the Opponents is the impact of the new product patent regime on PLHAs' access to safe, effective and affordable HIV/AIDS treatments.
  
3. The HIV/AIDS epidemic poses one of the greatest challenges to global public health today, but even more so for developing countries, including India. Over 40 million people worldwide are infected with the HIV virus, with an estimated 5.2 million in India. Although medical treatments, such as the patent application in case, can help infected people to manage this lifelong condition, this is only possible if people can afford to access such treatments. In the developing world, access to key treatments and, therefore life itself, is only possible if these treatments are priced affordably. While true innovations for new treatments can help towards offering new hope for HIV sufferers around the world, they also take away that opportunity. Patents granted for 20 years on such treatments allow the "inventor" not only to dictate the prices, which are nearly always beyond the income of the majority of people in the developing world and India, but also determine who can manufacture these essential medicines. This reality creates a difficult situation between the patents system and the matter of life and death.

4. As a result, patents on “inventions” such as the one that is the subject of this opposition, should only be granted where they do not harm the public’s needs, but also science and development itself. All too often in the pharmaceutical sector, patents are granted for minor and inconsequential changes to known substances in order that the company, which is the proprietor of the already known patented substance, can unduly extend its monopoly and continue making unjust profits. Such practice does not fit within the founding philosophy of patents, namely real innovation and development of the art in question for the benefit of the public at large.
  
5. In view of such practices, the duty on Patent Offices, such as this one, is to ensure that they act as the safety net to ensure that only patents for genuinely new innovations are granted. As such, the Patents Act offers this Patent Office the safeguards and tools, such as s3(d), to ensure that non-meritorious patents that are not true inventions are weeded out not only for the public’s benefit, but also for science and development. However, the failure to do so in matters such as the one in question could lead to the loss of millions of lives tomorrow and in the future to come, which ultimately could easily have been prevented.
  
6. Taking the above comments into account, the Opponents have learnt that on 25 July 1997, the Applicant filed for a patent titled “Nucleotide Analogs” at this Patent Office, which was allotted Application No. 2076/DEL/1997 A (hereinafter ‘2076) and claims a priority date of 26 July 1996 from U.S Application No. 08/686838. ‘2076 was published for opposition in the

Official Journal of the Patent Office on 11 March 2005, a copy of which is attached as **Exhibit 1**, and which is understood to be currently under examination and has not as yet been granted.

7. '2076 is an application that claims an invention for compounds comprising esters of antiviral phosphonmethoxy nucleotide analogues with carbonates and/or carbomates. The compounds in '2076 are claimed as being useful as intermediates for the preparation of well known antiviral phosphonmethoxy nucleotide analogues, in particular for the acyclic nucleoside phosphonate (9-[(R)-2-(phosphonolmethoxy)propyl]adenine (otherwise referred to as PMPA or by the generic name Tenofovir), as well as for use in the efficient oral delivery of such analogues. Such intermediates as claimed in '2076 are otherwise known as prodrugs of their parental compounds.
  
8. Acyclic nucleoside phosphonate analogues such as PMPA were first discovered in 1985 and were published in the patent EP 0206459 (hereinafter '459), on 30 December 1986, attached as **Exhibit 2**. '459 discloses the compounds 9-(phosphonylmethoxy-alkyl) adenines of the general formula as shown in claim 1 on page 20. The compounds disclosed in '459, in particular page 8 of '459, show an active ingredient of an antiviral medication and which can be converted into compounds with antiviral effect. Example 2 on page 11 and Table 1 on page 19 clearly define the active antiviral compounds, including PMPA. Indeed, as admitted by the Applicant at lines 20-24 on page 4 of '2076, "the parental compounds which have the structure  $\text{AOCH}_2\text{P}(\text{O})(\text{OH})_2$  are well known and have demonstrated antiviral activity.

Per se they are not part of this invention.” Some of the parental compounds disclosed in **Exhibit 2** have proved useful in the treatment or prophylaxis of one or more viral infections in man, animals, including particularly retroviruses, HIV, SIV and GALV and hepadnaviruses.

9. The Applicant’s claimed invention in ‘2076 may be summarised as follows:
  - a) Claim 1 relates to an ester or an amidate of an antiviral phosphonmethoxy analogue of Formula (1a) and the salts, hydrates, tautomers and solvates thereof covering a broader group of compounds.
  - b) Claim 2 relates to the compound of claim 1 but is narrower in its coverage wherein various possible functional groups mentioned in the general Formula 1(a) are described.
  - c) Claims 3-25 relate to various compounds resulting from different combinations of various functional groups covered by the general formulas in Claims 1 and 2.
  - d) Claim 26 relates to a method of treatment for treating a patient infected with a virus or at risk of a viral infection with a therapeutically effective amount of the compound claimed in Claim 1.

- e) Claim 27 relates to a method for preparing a compound of formula 1(a), as claimed in Claim 1, by reacting the diacid of a phosphonmethoxy nucleotide analogue with  $L-CH(R_2)OC(O)X(R)_n$  wherein L is a leaving group.
- f) Claim 28 relates to a method of preparing a compound of formula (1), as claimed in Claim 2, by reacting  $L-CHR_2-O-C(O)-OR$  wherein L is a leaving group with the compound of formula 6.
- g) Claim 29 relates to the proportion of one of the reactants used in the method for Claim 30.
- h) Claim 30 relates to the reaction parameters and the solvent used for the method claimed in Claim 31.
- i) Claim 31 relates to the method used for recovering the compound claimed in Claim 1 through salt formation and precipitation of the salt.
- j) Claim 32 relates to the acids that can be used for obtaining salts for the method claimed in Claim 31.
- k) Claims 33 and 34 are omnibus claims for compounds claimed in Claims 1 and 2 for formulas 1 and 1(a).

- l) Claims 35 and 36 are omnibus claims for methods of preparing compounds in Claims 1 and 2 for formulas 1 and 1(a).

10. The Opponents have closely studied the specification and Claims made by the Applicant in '2076 and strongly believe that the claimed invention is not patentable under the following grounds of s25(1) of the Act:

- a) s25(1)(e) – that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step having regard to the matter published as mentioned in clause (b) (of s25(1)) or having regard to what was used in India before the priority date of the applicant's claim.
- b) s25(1)(f) – that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act, in particular under sections 3(d) and 3(i).
- c) s25(1)(h) – that the applicant has failed to disclose to the Controller the information required by s8 or has furnished the information that in any material particular was false to his knowledge.

Accordingly, as permitted under s25(1) of the Act and Rule 55(1) of the Rules, which allow for a representation of opposition to be filed by any person after publication but before the grant of a patent, the Opponents submit their representation of opposition to '2076 on the grounds set out below. Furthermore, as '2076 was filed at this Patent

Office (New Delhi), the Patent Controller of the said office has the authority to hear and decide on this opposition.

### **GROUND**

The Opponents submit their opposition on the following grounds:

**Claims 1-25 and 27-36 of the invention are not patentable under sections 2(j), 2(ja) and 25(1)(e) of the Act**

11. Claims 1-25 and 27-36 of '2076 do not meet the requirements of the definition of an invention as provided in sections 2(j) and 2(ja), and are, therefore, objected to under s25(1)(e). Section 2(j) clearly states that an invention means a new product involving an inventive step. Section 2(ja) qualifies the meaning of inventive step as being a "feature of an invention that involves a technical advance compared to existing knowledge and that makes the invention not obvious to a person skilled in the art." Section 25(1)(e) defines the abovementioned sections for the purpose of an opposition as "an invention which is obvious and clearly does not involve any inventive step having regard to matter published as mentioned in s25(1)(b) or having regard to what was used in India before the priority date of the applicant's claim."
  
12. As already briefly discussed in paragraph 7 above, '2076 claims an invention for compounds comprising esters of antiviral phosphonmethoxy nucleotide analogues with carbonates and/or carbomates, which are suitable for the



efficient oral delivery of such analogues. Therefore, the problem which the Applicant claims to have solved is to have invented an ester prodrug for nucleotide analogues, in particular PMPA, in order to improve the poor oral bioavailability of such compounds so as make them suitable for oral delivery. However, the Opponents believe that the Applicant's claimed invention of developing ester prodrugs for nucleotide analogues in order to improve their oral delivery does not amount to a technical advance compared to existing knowledge and, therefore, lacks any inventive step. The Opponents contend that the steps taken by the Applicant would have been obvious to a skilled person in the art given the extensive published literature before the priority date of '2076, 26 July 1996, which show the successful adoption of esters in oral drug discovery (prodrug) programmes for nucleotide analogues.

13. The prodrug approach of preparing esters of compounds with limited oral bioavailability in order to improve transcellular absorption, including lipophilicity, half life, site specificity, chemical instability, toxicity and even poor patient acceptance, has been known in the pharmaceutical field since the 1950s, gaining prominent attention in the 1970s. During this period, numerous prodrugs have been designed and developed (including for nucleotide analogues) and suitable esters for the ideal prodrug candidate have been identified. By way of example of the suitable prodrug candidates which were known before the priority date of '2076, the Opponent's refer to the publication by Robert Notari, *Prodrug Design*, Pharmaceutical Therapy, Vol.14, pages 25-33, (1981), attached as **Exhibit 3**. On page 27 of the said publication, under the heading "Prodrug Candidates and Prodrug

Conversion”, Notari, citing the publication of Sinkula A.A. and Yalkowsky S.J, *Rationale for design of biologically reversible drug derivatives: prodrugs*, Journal of Pharmaceutical Science. 64, pages 181-210, (1975), summarises the possible enzyme reversible prodrug linkages as: "aliphatic esters, CARBONATE esters, hemiesters, phosphate esters, sulfate esters, amides, amino acids, azo linkages, CARBAMATES, phosphamides, glucosiduronates etc.” The author then proceeds to state that “Although the list is short the list of prodrug linkages commonly employed is much shorter. By far the most widely used prodrug linkage is that of an ester wherein the original drug provides either the carboxylic acid or hydroxyl group. Add to this carbonates phosphates and hemiesters and one has accounted for the majority of prodrugs." As can be seen from the above, not only were carbonate and carbamate esters already known as useful prodrugs linkages, but also that the list of esters commonly employed as prodrug linkages is short.

14. Since the discovery of the antiviral therapeutic potential of nucleosides and nucleotide analogues (see for example **Exhibit 2**) it has been identified that such compounds have shortcomings in terms of low permeability and bioavailability given the negative charge(s) on the phosphorous. This is the particular problem that the Applicant claims to have solved in ‘2076. However, prior to the priority date of claimed invention in ‘2076, ester prodrugs improving the oral bioavailability for other nucleoside and nucleotide analogues with antiviral qualities have been developed. This has been particularly well documented by Robert Jones and Norbert

Bischofberger, *Minireview: nucleoside prodrugs*, Antiviral Research 27, pages 1-17, (1995), attached as **Exhibit 4**. On page 2 of **Exhibit 4**, under the heading “Introduction”, the authors state that “nucleoside and nucleotide analogs, despite their therapeutical potential for the treatment of viral diseases, have short comings in terms of low permeability and bioavailability given the negative charge(s) on the phosphorous and 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.”

15. In particular, page 5 of **Exhibit 4** discloses the ester prodrug of bis(pivaloyloxymethyl) (otherwise known as bis(POM)PMEA), as well as a host of other lipophilic esters, for Adefovir (9-[2-(phosphonmethoxy)ethyl]adenine (otherwise known as PME A), which is structurally similar to the nucleotide analogue PMPA. Such ester prodrugs of PME A are discussed at more length in Starrett et al, *Synthesis, Oral Bioavailability Determination and in vitro evaluation of prodrugs of the antiviral agent (9-[2-(phosphonmethoxy)ethyl]adenine (PME A)*, Journal of Medicinal Chemistry, 37, pages 1857-1864, (1994), attached as **Exhibit 5**, and Farquhar et al, *Synthesis and antitumor evaluation of bis[pivaloyloxy)methyl]2'-deoxy-5-flourouridine 5' monophosphate(FdUMP): A strategy to introduce Nucleotides into cells*, Journal of Medicinal Chemistry, 37, pages 3902-3909, (1994), attached as **Exhibit 6**.

16. Other relevant publications revealing the ability of different esters to enhance the oral bioavailability of nucleoside and nucleotide analogues include:

EP 0694547 (hereinafter '547) published as an application on 31 January 1996, attached as **Exhibit 7**. '547 represents Valganciclovir, the L-valinate ester prodrug for Ganciclovir, a nucleotide analogue having limited oral bioavailability. '547 claims the L-valinate ester in Claim 1 and clearly demonstrates on page 21 of the said specification the improved oral bioavailability of Ganciclovir as a result of the ester prodrug. Although not a prior publication, in McIntee et al, *Probing the Mechanism of action and decomposition of amino acid phosphomonoester amidates of antiviral nucleoside prodrugs*, Journal of Medicinal Chemistry, 40, pages 3323-3331 (1997), attached as **Exhibit 8**, the authors on page 3323 under the heading "Introduction" while citing the earlier work of Wagner et al, *Aromatic amino acid phosphoramidate di- and trimesters of 3'-azido-3'-deoxythymidine (AZT) are non-toxic inhibitors of HIV-1 replication*, Bioorganic Medicinal Chemistry, 5, 1819-1824, (1995), state that "of the various prodrug approaches, amino acid phosphoramidate derivatives have shown promise as potent antiviral agents, since in some cases they have exhibited enhanced antiviral activity and reduced cytotoxicity when compared to the parent nucleoside."

17. Given the plethora of prior publications on improving the oral delivery of compounds, including for nucleotide analogues, the Opponents believe that the Applicant has simply practised what is common in the art, with the

knowledge that there would be more than a reasonable expectation of success. As it was already known that the ionic nature of a nucleotide analogue such as PMPA limited its permeation across the epithelial membrane (see for example **Exhibit 4**), it would have been obvious to the Applicant to prepare a selection of esters, including carbonates and carbamates, to block these negative charges in order to liberate the nucleotide at a specific site. The Opponents contend that an ordinarily skilled person versed in the practice of pharmacokinetics and metabolism would have known to link a bulky ester prodrug such as tertiarybutyle carbonate, or isopropyl carbonate. By linking an ester such as carbonate, the Applicant would have known that it could increase lipophilicity of the parent compound, thus allowing the drug to penetrate across the lipophilic membrane, improve bioavailability, and increase the half life of the drug in circulation. Indeed, as already set out in **Exhibit 3**, the list of prodrug linkages commonly used in the field is not such a long one, which would have meant that the Applicant may have tested only a handful compounds in very little time before selecting that the carbonate and carbomate esters achieved the desired result.

18. More significantly, given that the Applicant had already selected and tested a number of esters in achieving the improvement in oral bioavailability for the anionic and negatively charged nucleoside PMEAs, which resulted in the selection of the ester prodrug bis(POM)PMEA (see **Exhibits 4, 5 and 6**) (it should be noted here that Gilead is also the proprietor of the compounds Adefovir and product Adefovir Dipivoxil), it is more than likely, and therefore obvious, that the Applicant would have known which esters would

achieve the same result for the similarly structured nucleotide analogue PMPA. Indeed, the only difference between bis(POM)PMEA and the claimed invention in '2076, is that the Applicant switched hydrogen with methyl (the alkyl group) and substituted the tertiarybutyl linkage in carbonate to an isopropyl linkage. Such changes would have been obvious to a person skilled in the practice pharmacokinetics and metabolism.

19. Therefore, the claimed invention in Claims 1-25 and 27-36 of '2076 simply relate to the selection and preparation of esters from a group of prodrug linkages which are well known and practiced in the art in order to improve the oral bioavailability of parent compounds. Although some jurisdictions, which have less stringent patent laws, may allow what are known as selection patents from an already disclosed group of compounds, there are many countries which deem such practice obvious and simply a way to extend the life of a patent. The Opponents contend that this Patent Office has the ability to set the standard of patentability so as not grant to such obvious patenting for the benefit not only of public health but also genuine inventions. By doing so it would still be seen to be compliant with TRIPS as the threshold for what an invention can be is entirely up to each national Member.

**Claims 1-25 and 27-36 of the invention are not patentable under sections 25(f) and 3(d) of the Act**

20. In the alternative and without prejudice to the arguments set out in paragraphs 11-19 above, the Opponents rely on s3(d) read with sections 2(j), 2(ja) and 25(1)(f). Section 3(d) sets out that a “*mere discovery of a **new form of a known substance** which does not result in the enhancement of the known efficacy of that substance*” does not amount to an invention and is not patentable under the Act. The ‘Explanation’ for s3(d) provides further clarification in that “*salts, esters, ethers, polymorphs....combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy*”.

21. Based on a plain reading of s3(d), it is quite clear under that any new discovery of an ester for a known compound is not patentable as an invention. Therefore, on such reading, the Applicant’s claim to inventing esters for nucleotide analogues, including PMPA, is not patentable. Indeed, the Opponents contend that one of the purposes of s.3d is to safeguard against the obvious practice of selection patents and the claiming of patents for the discovery of esters, salts and other intermediates that are commonly used in the pharmaceutical industry to extend the patent life of known substances.

22. However, the Opponents recognise that s.3d does contain a proviso with respect to whether the discovery of new forms of known substances,

including ester prodrugs for known compounds, are to be considered inventions. That proviso is the need for the Applicant to show that the new form of the known substance, which it claims to have discovered, results in the “enhancement of the known efficacy of that substance.” More particularly, the proviso in the section states “esters of a known substance shall be considered to be the same substance unless they differ significantly in properties with regard to efficacy”. Therefore, it is fair to say that the key determinations for assessing whether the new form of a known substance (the esters of the nucleotide analogues as is the case in point here) can be deemed patentable is to define and understand the terms “differ significantly in properties” and “efficacy” in the context of the application in question.

23. Taking the term “efficacy” first, it is appropriate to state that s3(d), and its supporting explanation, is directed at and particularly relevant to pharmaceutical product patent applications such as ‘2076. On this basis, it would seem logical that “efficacy” be interpreted according to a standard and uniform definition as used in the pharmaceutical industry and field of pharmacology. Therefore, adopting the above rationale approach, the Opponents believe that for the purpose of determining whether ‘2076 meets the requirement of efficacy one needs to look at: (1) how the pharmaceutical industry commonly defines or uses the term “efficacy” in relation to pharmaceutical products and pharmacology; (2) the known activity of the active substance in question, in this case PMPA and (3) how the claimed improvements in ‘2076, namely the alleged improvement in the oral bioavailability of the active parent compounds and their stability, sit in



relation to points (1) and (2) and whether those improvements differ significantly in properties with regard to efficacy.

24. The Opponents believe a sensible starting point for the first point in question is to provide a standard and commonly used pharmacological definition for “efficacy”. A useful and standard definition for “efficacy” is provided in Bowman’s Dictionary of Pharmacology (1986) as being “the capacity of an agonist to initiate a response once it occupies receptor sites.” Another useful and more detailed definition is that provided in the attached **Exhibit 9**, which broadly defines efficacy as “referring to the capacity of a drug to produce an alteration in a target cell/organ after binding to its receptor.” **Exhibit 9** also states that efficacy is related to “intrinsic efficacy”, which broadly means “the property of a drug that determines the amount of biological effect produced per unit of drug-receptor complex formed.” For a definition of “intrinsic efficacy” see attached **Exhibit 10**.

25. Taking the above standard definitions of efficacy, it is then a question of determining whether the alleged improvements claimed in ‘2076 differ significantly in properties with respect to efficacy over the known active substance(s) in ‘2076. Using the standard definitions of “efficacy” as provided in paragraph 22 above and **Exhibits 9** and **10**, the Opponents contend that the Applicant has failed to meet the standard required to claim an invention for Claims 1-25 and 27-36. This is clearly obvious by the fact that the previously known active substance PMPA and its known antiviral activity or therapeutic moiety, still remains the same after binding its receptor site, even when administered as an ester prodrug bis(POC)PMPA. Even though

the Applicant may argue an improvement in the oral bioavailability of PMPA has been achieved (which the Opponents will discuss and counter in more detail below) it has to be recognised that such a claimed improvement does not improve the actual efficacy of the antiviral activity of the parent compound. This is because the ester prodrug is cleaved back to PMPA without any change in the viral load of PMPA. Viewed in light of the standard definition of “efficacy” provided herein, the invention claimed in ‘2076 amounts to nothing more than a new form of a known substance but which fails to meet the normative standards of “efficacy”.

26. If anything, the Applicant can only point to an improvement in oral bioavailability of parent compounds such as PMPA as a result of the “invented” ester prodrug. Assuming without admitting that an increase in the oral bioavailability of a parent compound is the standard for meeting the “significantly differ in properties with regard to efficacy” requirement as set out in s3d, the Opponents believe that the Applicant has failed to clear this hurdle also. Moreover, the Opponents believe the Applicant has deliberately used ambiguous language and test data in the specification in order to demonstrate an improvement in the oral bioavailability of PMPA when administered orally as the ester prodrug.

27. At lines 19-22 on page 32 of ‘2076, the Applicant claims that “In addition, the optimal compounds of this invention should have a bioavailability in beagle dogs (as set forth in more detail below) that exceeds about 20%, preferably, about 30%. The Applicant then sets forth in Example 15, on pages

56-60 of the specification, the steps taken to test the oral bioavailability of PMPA and PMPA Carbonates in Beagle Dogs. At lines 5-8 on page 59 of '2076, the Applicant asserts that "Oral bioavailability of t-Bu, 3-pentyl, isopropyl, Et carbonate parameters were compared by unpaired t-tests...A P value of  $\leq 0.05$  was considered significant." The Applicant then produces in Table 1, on pages 61-63 of the specification, a summary of the test results for the PMPA Prodrug. It should be noted here that Beagle dogs are deemed to represent the closest model to human testing in the pharmaceutical/pharmacology field. More importantly, for the purpose of analysing the test data and the Applicant's claims of improved oral bioavailability in '2076, such data should be assessed in light of preclinical studies that have shown Tenofovir (PMPA) as having an **oral** bioavailability of 17.1% in Beagle dogs (*emphasis added*). The Opponents refer to page 1521, left hand column, second paragraph of the publication by Fung et al, *Tenofovir Disoproxil Fumarate: A Nucleotide Reverse Transcriptase Inhibitor for the Treatment of HIV Infection*, Clinical Therapeutics, Vol 24, No. 10 (2002), attached as **Exhibit 11**. It should be noted that the authors of the above publication cite from the publication by Shaw et al, Metabolism and pharmacokinetics of novel oral prodrugs of 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs, *Pharmaceutical Research*, 14, pages 1824-1829, (1997).

28. Considering the results set out in Table 1 first, it is immediately noticeable that the Applicant has not provided any data for the existing oral bioavailability of PMPA and has omitted a large number of meaningful data,

such as pH2 data, for many of the prodrugs tested, in particular Bis-isopropylCOM PMPA (otherwise known as bis(POC)PMPA). As a result it would not be possible for this Patent Office to determine, for the purpose of s.3d, whether there has been any improvement in the oral bioavailability of PMPA when given as PMPA Carbonates in Beagle dogs. Therefore, on this issue alone, the application should be dismissed or the Applicant be put to strict proof.

29. It is also noticeable that the test results are broad in their ambit, meaning that there is a possible “lower” figure and a “higher” figure reflecting the oral bioavailability achieved. For example, in the Table on page 62, the results show Bis-isopropylCOM PMPA achieving an oral bioavailability of  $35\pm 14.7$ . Given such a wide variation in the animal data, the test results showing a reading of  $35\pm 14.7$  could be interpreted as either proving an oral bioavailability of 20-21% ( $35-14.7$ ) or as high as 49-50% ( $35+14.7$ ). However, the Applicant at lines 19-22 on page 32 of the specification offers a vague clarification by admitting that “In addition, the optimal compounds of this invention should have a bioavailability in beagle dogs (as set forth in more detail below) that exceeds about 20%, preferably, about 30%.” Nevertheless, use of terms such as “should”, “about”, “that exceeds” and “preferably” are all deliberately ambiguous and raise serious question marks as to what the actual figure is. Indeed, the use of the terms “should” alongside “exceeds” and “preferable” suggests that a figure under 20% is often possible, whereas the higher figure, being preferable, is not regularly attained. The above data and claims are even more questionable when one

considers the Applicants statement in relation to the P test at lines 5-8 on page 59 which claims a P value of  $\leq 0.05$  was considered significant. According to the Opponents understanding of P tests, the tests may have displayed varying degrees of improvement in the oral bioavailability studies in the Beagle dogs, and indeed this seems to be the case from some of the results in Table 1. For example, one animal may have shown an oral bioavailability of PMPA of 17%, another 20%, another 22%, another 25% and another say 80%. Therefore, aside from the last figure of 80%, which would be considered to be an anomaly, the mean average data would have shown the oral bioavailability to be around 21%. However, when introducing the results of the test showing an increase of 80%, the mean average shoots up to 41%.

30. Therefore, taking the above information in hand, it is more than likely that the mean average of the P test was not as significant as the Applicant claims, and at best PMPA Prodrug showed an oral bioavailability of between 21%-25%. When comparing this “improvement” to the known 17.1% oral bioavailability of PMPA in Beagle dogs, as shown in **Exhibit 11**, the Applicant cannot claim that the ester prodrug of PMPA shows a significant difference in properties with regard to efficacy, as the “improvement” in oral bioavailability is nominal at best. Even if the Applicant is given the benefit of doubt and can show the “preferable” figure of an oral bioavailability of 30%, such an increase over the known oral bioavailability of PMPA is still not significant with respect to efficacy. As such, by the standards required of s3d and even normal bioequivalence standards, the known compound PMPA and the ester

prodrug as claimed in '2076 are the same substance or essentially similar drugs. To that end the Applicant's "invention" is not patentable under s3d.

31. The Opponents also point to the recent decision of the Chennai Patent Office in *Cancer Patients A.J Association, India v Novartis AG* (25 January 2006), attached as **Exhibit 12**, which serves as a precedent for this Patent Office. On page 4, paragraph 3 of that decision, the Assistant Controller clearly held that an increase of (>30%) bioavailability between the free base and the beta-crystal form of imatinib mesylate (which was the subject matter of the patent application), including the difference in their solubility in water, did not amount to an improvement in efficacy. Therefore, it can be conclusively stated that '2076 does not meet the required standard to show efficacy.

**Claim 26 of the invention is not patentable under sections 25(f) and 3(i) of the Act.**

32. Under s3(i), "any process for the medicinal, surgical, curative, prophylactic [diagnostic, therapeutic] or other treatment of human beings" shall not be considered an invention. Claim 26 amounts to nothing more than a therapeutic method, claiming the process of oral administration of a therapeutically effective quantity of a composition to a patient and as such is caught by s3(i) and does not amount to an invention.

**Claims 1-36 of the invention are not patentable under the sections 25(h) and 8 of the Act.**

33. Section 8(1)(a) and (b), read with Rule 12, makes it an obligation on the applicant to keep the Controller informed of the details of an application which is being prosecuted in another country and which is considered to be the same as the invention applied for in India. This obligation should be met by the Applicant within 3 months of the date of filing (as expressed by the relevant Patent Rules at the time, now amended to 6 months under the 2006 Amendment). Section 8 also requires the Applicant to provide an undertaking to keep the Controller informed of other application(s) being prosecuted up to the date of grant of the said patent in India. Section 25(1)(h) incorporates the requirements of s8 as a ground of opposition to the grant of a patent. Based on the above, the Opponents question whether the Applicant has provided this Patent Office with the information and particulars of the equivalent foreign applications that the Applicant is currently prosecuting.

34. In particular, the Opponents are aware from its searches and enquiries that the Applicant has applied to patent the same invention claimed in '2076 in China, under Chinese Application No.CN1244200A, titled "Nucleotide Analogs" and which claims priority from U.S Application No. 08/686838. According to the Opponents searches and enquiries, it is understood that Chinese Application No.CN1244200A is still pending under examination. The Opponents attach as **Exhibit 13** a patent search of 29 August 2006 and the relevant patent kind codes which shows Chinese Application

No.CN1244200A being classified as “A”, meaning that the application is an “unexamined application open to public inspection”. The Opponents seriously doubt whether the Applicant has informed this Patent Office of the status of its equivalent Chinese application. As a result, any failure by the Applicant to meet its obligations under s8 is a strict ground to refuse ‘2076 in its entirety.

35. In the event that this Patent Office does not take the view of the Opponents, the Opponents ask to be kept informed throughout these proceedings of whether the Applicant has provided this Patent Office with the required details of matters relating to the its corresponding application in China and any other pending application.

Based on the grounds set out in paragraphs 11-35 above, the Opponents request that Application No. 2076/DEL/1997 A be refused in its entirety. As permitted under Section 25(1) of the Act and Rule 55(1) of the Rules, the Opponents request that this Patent Office informs the Opponents immediately of any response filed by the Applicant to this opposition and also grant the Opponents a hearing in the above matter. The Opponents also request the right to be able to submit further evidence, if necessary, in order to further substantiate the grounds already raised in this representation.



Dated 5 day of September 2006

For and behalf of the Indian Network for People Living With HIV/AIDS (INP+)

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For and behalf of the Delhi Network of Positive People (DNP+)

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Our address for service in connection with these proceedings is:-

Indian Network for People Living With HIV/AIDS (INP+) / Delhi Network of  
Positive People (DNP+)

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To:

The Controller of Patents

The Patent Office, NEW DELHI