

THE PATENTS ACT, 1970
UNDER SECTION 25 (1)
REPRESENTATION OF OPPOSITION

In the Matter of an application for Patent no.
3383/DELNP/2005 filed on 29/07/2005

And

In the Matter of representation of opposition
u/s 25(1) of the Patents Act, 1970 as amended
By Patents (Amendment) Act, 2005

And

In the Matter under rule 55 of the Patent rules,
2003 as amended by the Patents
(Amendment) rules, 2006.

GILEADSCIENCES,INC,.....Applicant
M/s. CIPLA LIMITED.....Opponent

Hearing Held on 25th August, 2008

Present:

G. Nataraj.....Agents for the Applicant

Dr.Gopakumar G. Nair.....Representative for Opponent

Order

M/s CIPLA LTD., an Indian Public Limited Company, incorporated in Mumbai, India, having their registered office at 289, Bellasis Road, Mumbai Central, Mumbai - 400 008. (hereinafter referred to as the Opponent), filed an opposition by way of representation under Section 25(1) of the Patent Act, 1970 and Rule 55(1) of the Patent Rules, 2003 as amended by patent amendment rules 2006 to the grant of an application for patent filed 29th July,2005 by GILEAD SCIENCES, INC of 333 Lakeside Drive, Foster City, California 94404, United States of America (hereinafter referred to as the Applicant) for the invention titled as "COMPOSITIONS AND METHODS FOR COMBINATION ANTIVIRAL THERAPY"

As per the records the Application No. 3383/DELNP/2005 has a corresponding PCT International Application No PCT/US2004/000832, having Publication No WO/2004/064845, and International filing date of 13th January, 2004. The application is claiming priority from US Application No. 60/440,308 filed on 14th January, 2003 and US Publication no 2006/0246130 A1 is the National Phase Application of PCT International Application No PCT/US2004/000832.

It is further observed that original application filed was having 58 no's claims which were subsequently reduced to 19 no's upon transmission of first examination report.

Both parties made lengthy submissions to their claims on non patentability or patentability to the subject matter of this impugned patent Application.

Now after going through the submissions in detail, I shall reproduce, discuss, analyze and categories the vital submissions on the various grounds taken by the opponent so as to conclude upon my findings in this matter.

LACK OF NOVELTY

PRIOR PUBLICATION (Section 25 (1)(b)),

PRIOR CLAIMING (Section 25 (1)(c)).

Opponent's Submissions:

The agent for opponent has submitted that in the PCT International Application No. PCT/US2004/000832 (WO/2004/064845), which is related to the present Indian Application, has an International Search Reports (ISR) dated 18th June, 2004 mailed on 12th July, 2004 and 5th August, 2004 issued by European Patent Office (International Search Authority) (**Annexure V** and **Annexure VI**).

The said Search Reports has 11 (eleven) citations out of which 5 (five) are 'X' category citations in relation to 1 to 58 claims of the application. These citations are of particular relevance in this case because ISR describes 'X' category citations as those document

which anticipates the alleged invention of the Applicant. The Opponent quote 'X' category from the ISR as follows. *"the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document taken alone"* ('X' category citations).

The Documents cited in the PCT Search Report are reproduced below:

D1: RISTIG MARIA B ET AL: "Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus-coinfected individuals for whom interferon-alpha and lamivudine therapy have failed."

JOURNAL OF INFECTIOUS DISEASES, Vol 186, no. 12,

15 December 2002 (2002-12-15), pages 1844-1847,

XP002284897 ISSN: 0022-1899 Abstract

page 1844, column 2 Second last paragraph:

"Subjects"

page 1845, column 25 last paragraph before "Discussion"

D2: MURRY, JEFFREY P ET AL: "Reversion of the M184V mutation in simian immunodeficiency virus reverse transcriptase is selected by tenofovir, even in the presence of lamivudine" JOURNAL OF VIROLOGY, 77(2), 1120-1130 CODEN:

JOVIAM; ISSN: 0022-538X, 12 January 2003 (2003-01-12), XP002284898 page 1126, figure 2 page 1129, column 1. paragraph 2

D3: "Anti-HIV drug updates—three drugs on the near horizon." PROJECT INFORM PERSPECTIVE. JAN 2003, no. 35, January 2003 (2003-01).

pages 4-7, XPOO1181983

page 6, column 2, paragraph 3 - page 7, column 2, paragraph 3

D4: FUNG HORATIOBETAL- "Tenofovir disoproxil fumarate: A nucleotide reverse transcriptase inhibitor for the treatment of HIV infection."

CLINICAL THERAPEUTICS, vol. 24 no. 10, October 2002 (2002-10),

pages 1515-1548, XP002285091 ISSN: 0149-2918 page 1533, column

1, paragraph 2 page 1542, table VIII

D5: MULATO ASETAL: "Anti-HIV Activity Of Adefovir (PMEA) And PMPA In Combination With Antiretroviral Compounds: In Vitro Analyses"

ANTIVIRAL RESEARCH, ELSEVIER SCIENCE BV, AMSTERDAM, NL, vol. 36, no.

2, November 1997(1997-11), pages 91-97, XP000890091

ISSN: 0166-3542 page 93, column 2, paragraph 2 - page 95, column 1, paragraph 2 page 94, fig 1

D6: WO 00/25797 A (BARRY DAVID ; ROUSSEAU FRANCK (US); FURMAN PHILLIP A (US); PAINTER GEO) 11 May 2000 (2000-05-11) page 5, line 5-12 page 15, lines 1-24 claims 5, 10 and 20

Hence, it is submitted that the prior art disclosures having 'X' category remark by the ISA (International Search Authority) negates patentability criteria and the alleged Patent Application deserves to be rejected.

The Opponent further submitted a copy of the written Opinion of the International Searching Authority (PCT Rule 43bis.1) recorded on 8th July, 2005 and issued by European Patent Office. (Annexure VII). References as made in the report are quoted as below.

The alleged application does not meet the criteria of novelty as the subject-matter of claims 1-58 is not an invention under section 2(1)(j) of The Patents Act, 1970. The opponent quoted that :

D1 discloses the use of tenofovir disoproxil fumarate (TDF) in patients receiving lamivudine (3TC) or emtricitabine (FTC) (see page 1844, column 2, Second last paragraph). Although this document relates mainly to the treatment of the hepatitis B in HIV/HBV co-infected patients, it also reports that there was an anti-HIV activity (see page 1845, column 2, last paragraph before "Discussion").

D2 shows studies on the appearance of resistances in SIV when using tenofovir (PMPA) with 3TC or PMPA with FTC (see the passages mentioned in the search report).

D3 discloses that there is the intention of combining PMPA with FTC in a single pill (see page 7, column 2, last paragraph).

D4 discloses the use of TDF in combination with 3TC for the treatment of HIV infections (see the passages mentioned in the search report).

D5 teaches that the combination of PMPA or adenovirus (PMEA) with 3TC induces an additive inhibition of the HIV replication in vitro.

D6 discloses the combination of FTC with PMEA for the treatment of hepatitis B. PMEA is mentioned in the description of the present patent application to be functional derivative of Tenofovir (see page 11, lines 15-18).

Therefore, the subject-matter of present claims 1-58 cannot be considered novel in the light of documents D1-D5.

The Opponent prayed that the application for grant of Patent filed by the Applicant be rejected on the ground of existence of prior publications and also those listed in the International Search Report (**Annexure V**) and Final Rejection (**Annexure XIX**), in respect of the alleged invention of the Applicant under Section 25(1) (b) of The Patent Act, 1970.

The Opponent submitted the Indian National Phase Application No. 00698/KOLNP/2005 A titled "DIOXOLANE THYMINE AND COMBINATIONS FOR USE AGAINST RESISTANT STRAINS OF HIV" filed by The University Of Georgia Research Foundation & Emory University on 21/04/2005 and published on 24/02/2006, claiming priority from US Patent Application No. 60/431,812 filed on 09/12/2002 anticipates the alleged invention of the applicant. (**Annexure IX**).

The above Indian National Phase Application discloses the use of a dioxolane thymine compound for use in the treatment of HIV infections which exhibit resistance to 3TC and/or AZT. The compounds according to the present invention are combined with agents selected from (-)-FTC (Emtricitabine), Tenofovir (PMPA), EFV (Efavirenz). 3TC (Lamivudine), AZT (Zidovudine), ddI (Didanosine), ddC (Zalcitabine). Abacavir (ABC), D-D4FC (Reverset), D4T (Stavudine), Racivir, L-D4FC, NVP (Nevirapine), DLV (Delavirdine), SQVM (Saquinavir mesylate), RTV (Ritonavir), IDV (Indinavir), SQV

(Saquinavir), NFV (Nelfinavir). APV (Amprenavir), LPV (Lopinavir), fuse on and mixtures thereof. Since the alleged invention as such is disclosed in the said Indian National Phase Application, the same stand prior published and hence, is ineligible for grant of Patent.

The Opponent further submitted that US Patent No. 6,194,391 titled "3'-AZIDO-2¹, 3'-DIDEOXYUR/DINE ADMINISTRATION TO TREAT HIV AND RELATED TEST PROTOCOL" filed by Emory University And Norvirio Pharmaceuticals Limited on

24/06/1999, claiming priority from US Application No. 60/090,552, filed on 24/06/1998, discloses a method of treating humans infected with HIV comprising administering CS-87 in combination with a second anti-HIV drug. The second anti-HIV drug is PMPA (Tenofovir) and/ or FTC (Emtricitabine), chosen amongst others. (**Annexure X**).

The Opponent further submitted that US Patent No. US 7,094,413 titled "COMBINATION THERAPY FOR TREATMENT OF HIV INFECTION", granted to Sangstat Medical Corporation and The Regents of the University Of California on 22/08/2006, claiming priority from US Patent Application No. 60/351,925 filed on 24/01/2002 The said US Patent discloses a method of treating an individual infected with HIV, comprising administering to an HIV infected individual a pharmaceutically effective amount of an immuno-modulatory peptide and at least one anti-retroviral agent chosen from Tenofovir and Emticitabine, amongst others.(**Annexure XI**).

The Opponent relied upon the prior art publications (**Annexure V to Annexure XVII**)

The Opponent requested to take these publications in the context of other sub-sections of Section 25(1) also. These prior publications destroy the Novelty and Inventiveness of the alleged invention.

The Opponent submitted that the application of the Applicant is ineligible for grant of Patent under Section 25 (1) (c) of The Patents Act, 1970

The Opponent relied upon the documents cited in the International Search Report (**Annexure V**), the Final Rejection (**Annexure XIX**) and the documents which have been published before the priority date of the said patent application and claim therein to oppose the grant of the patent on the grounds of prior publication.

The Opponent submitted that the Indian National Phase Application No. 00698/KOLNP/2005 A titled "DIOXOLANE THYMINE AND COMBINATIONS FOR USE AGAINST RESISTANT STRAINS OF HIV" filed by The University of Georgia Research Foundation & Emory University on 21/04/2005 and published on 24/02/2006, claiming priority from US Patent Application No 60/431.812 filed on 09/12/2002 anticipates the alleged invention of the applicant. (**Annexure IX**).

The above Indian National Phase Application discloses the use of a dioxolane thymine

compound for use in the treatment of HIV infections which exhibit resistance to 3TC and/or AZT. The compounds according to the present invention are combined with agents selected from (-)-FTC (Emtricitabine), Tenofovir (PMPA), 3TC (Lamivudine), AZT (Zidovudine), ddI (Didanosine), ddC (Zalcitabine), Abacavir (ABC), D-D4FC (Reverset), D4T (Stavudine), Racivir, L-D4FC, NVP (Nevirapine), DLV (Delavirdine), EFV (Efavirenz), SQVM (Saquinavir mesylate), RIV (Ritonavir), IDV (Indinavir), SQV (Saquinavir), NFV (Nelfinavir), APV (Amprenavir), LPV (Lopinavir), and mixtures thereof. Since the alleged invention as such is disclosed in the said Indian National Phase Application, the same stand prior published and hence, is ineligible for grant of Patent. The Opponent relied upon prior art publications **Annexure IX** to **Annexure XVII** having claims which overlap the alleged claims.

Applicant's Submissions:

Ld. Agent for Applicant submitted that the opponent relied upon several documents listed as hereunder:

Annexure V - International Search Report (ISR)

Annexure VI — Revised ISR

Annexure VII - Written Opinion of the International Search Authority (ISA)

Annexure VIII - International Preliminary Report on Patentability (IPER)

Annexure IX - Indian National Phase Patent Appl.No

00698/KOLNP/2005

Annexure X - US Patent No. 6,194,391 (Schmazi et al)

Annexure XI - US Patent No. 5,094,413 (Buelow et al)

Annexure XII - The Body (lover- The Complete HIV/AIDS Resource

Annexure XIII - US Patent No 4,808,716 (Hoi et al)

Annexure XIV - US Patent No 5,922,695 (Anmilh et al)

Annexure XV - US Patent No 5,047,407 (Belleau et al)

Annexure XVI - US Patent No 5,210,085 (Liotta et al)

Annexure XVII - US Patent No. 5,204,466 (Liotta et al)

Annexure XVIII - Amended transmittal of corresponding US application

Annexure XIX - Final rejection of US 2006/0246130 A1

None of the documents relied upon by the Agent for the opponent is even materially relevant to the patent application under opposition.

The Agent for Applicant submitted that to establish the ground of anticipation by prior publication leading to lack of novelty, the opponent must cite documents which were published before the priority date of the opposed application, in this case before January 14, 2003 as 3383/DELNP/2005 was

filed as a national phase application on 29 July 2005 from PCT International Application PCT/US2004/000832 claiming priority from US Provisional Patent Application No. 60/440,308 filed on 14 January 2003.

In addition, each of the cited documents must individually and unambiguously reach every element of the claimed invention. Mosaicing or combining two documents is not permissible to establish lack of novelty.

It was submitted that Indian Patent Application 698/KOLNP/2005 was published much after the priority date of the present application and therefore does not constitute prior art, let alone material anticipatory prior art.

The PCT Pamphlet corresponding to 698/KOLNP/2005 was published on June 24, 2004, over one year after the priority date of the present application and therefore does not constitute prior art, let alone material anticipatory prior art. Therefore reliance on this document to establish the ground of anticipation by prior publication under Section 25(1) (a) is incorrect and unfounded and contrary to the provisions of Section 25(1).

It was further submitted that US Patent 7,094,413 was published on August 22, 2006 almost three and half years after the priority date of the present application. Again, it is respectfully submitted that the said US Patent does not constitute prior art, let alone material anticipatory prior art. Therefore reliance on this document for the ground of anticipation by prior publication

under Section 25(1)(a) is incorrect and unfounded and contrary to the provisions of Section 25(1).

The Agent for Applicant submitted that reliance on the above two documents only establishes, if not the mala fides, the absence of knowledge of Indian patent law of the representers.

The representers relied upon the International Search Report and citations listed therein on corresponding PCT International Application PCT/US2004/000832 to allege lack of novelty.

The Agent for Opponent has failed to show which parts of which document listed in the ISR actually teach the claimed invention. The only submissions of the representers is that since the International Search Authority has listed these citations under the ground of lack of novelty, the invention of the present application does not have novelty. It is further submitted that a clear examination of the ISR will show that of the six documents mentioned by the representers, D4 is not cited in category X as alleged by the representers. The representers are actually mis-representing the statements in the ISR.

It was further submitted that the averments of the representers again show then-lack of knowledge of patent law or practice and that the ISR is not a binding document but is only of persuasive value and that each Patent Office has the jurisdiction and authority to make its own assessment of novelty and inventive step, which may even be different from the findings of the ISR.

In any event, it is respectfully submitted that none of the citations listed as D1 to D6 by the representers teach the claimed invention either individually or unambiguously.

It is a matter of record that patent application no.3383/DELNP/2005 had 58 claims of which claims 1-24 related to a method of treatment or prevention of the symptoms and effects of HIV infection by a composition of tenofovir disoproxil

fumarate (TDF) and emtricitabine (FTC) or their functional derivatives thereof, claims 25-41 related to a pharmaceutical formulation of TDF and FTC or their functional derivatives thereof along with one or more pharmaceutically acceptable carriers and excipients; claims 42-46 related to a patient pack comprising of above mentioned formulation and information insert containing directions and claims 47-58 provides chemically stable pharmaceutical oral dosage form of TDF and FTC further comprising a third anti-viral agent. It was further submitted that the claims now currently on file relate to a stable formulation of TDF and FTC with carrier and claims relating to method of treatment have been cancelled. It was submitted that none of the citations listed by the ISR actually specifically teach what is now claimed on the present application.

It was submitted that D1 discloses the use of tenofovir disoproxil fumarate (TDF) for treating chronic hepatitis B in patients who were co-infected with HIV and HBY and were receiving 3TC (lamivudine) or FTC treatment (emtricitabine) treatment D1 does not disclose a stable formulation of TDF and FTC and carrier. Therefore, the present invention is novel over D1 The Agent for Applicant submitted that D2 states that although the addition of PMPA to the FTC therapy induces a decrease in the virus loads in plasma, these loads eventually returns to pre-PMPA levels (Abstract, lines 17-20). All animals receiving this combination develop the K.65R mutation which is associated with resistance to both drugs. Further, this combination is unstable due to reciprocal catalytic hydrolysis of the two compounds The present invention, on the other hand, provides a stable co-formulation of TDF and FTC It is therefore respectfully submitted that D2 does not teach a combination of TDF and FTC and carrier and therefore does not destroy the novelty in the present invention.

It was submitted that the applicants have been informed by the editors of D3 that the January 2003 issue was sent out by mail and posted online between

January 28 and January 31, 2003. Thus, D3 was made available to the public after the priority date of January 14, 2003 and is therefore not a prior art document.

The Agent for Applicant submitted that D4 only discloses that TDF exhibits anti-HI\

activity in various HIV-infected cell lines when combined with other anti-retroviral agents. D4 does not teach the use of TDF and FTC and carrier in the claimed combination of the present application. Therefore document D4 does not constitute materially anticipatory prior art. Furthermore, D4 was cited in category Y in the ISR as having relevant to inventive step, and not on the ground of lack of novelty.

D5 teaches that the combination of PMPA with adefovir (PMEA) with 3TC induces an additive inhibition of the HIV replication in vitro. D5 does not teach the combination of TDF and FTC and carrier of the present application, and therefore does not constitute material or relevant anticipatory prior art.

D6 discloses a combination of FIC with PMEA for the treatment of hepatitis B. D6 does not teach the combination of TDF and FTC and carrier of the present application, and therefore does not constitute material or relevant anticipatory prior art.

The Agent for Applicant submitted that each of D1 to D6 actually teach various combinations of drugs other than those used in the present invention. Also, none of the documents D1 to D6 alone or in combination disclose a stable combination of TDF and FTC and carriers/excipients which substantially improve the stability of the combination.

It was further submitted that Annexures V to VIII relied on by representers are in International Search Report (ISR), Revised ISR, Written Opinion of the ISA and International Preliminary Report on Patentability (IPER), respectively. The representers state that ISR has 11 citations, of which 5 are 'X' category citations.

ISR actually has only 8 citations. Annexure VII refers to only 6 of these 8 citations. In paragraph 8(i)(a), the Representatives simply reproduced the documents as given in the ISR. In paragraph 8(ii)(a), the Representatives again simply reproduced the Written Opinion of the ISA. On this basis, the Representatives allege that the subject matter of the claims 1 to 58 of the present application cannot be considered novel in the light of D1 to D5 under Section 2(1)(j) and 2(1)(l) of The Patents Act and that they do not meet the catena of inventive step under Section 2(1)(ja). The representatives have not provided any reference to any portion of any of the cited documents to substantiate their allegation. It is submitted that this clearly establishes the mala fide nature of this representation and the absence of any technical analysis by the representatives.

The Representatives allegation in paragraph 8(ii)(C) and 8(iv) that the present application is not novel in view of the prior art cited in Annexures IX to XI, the Agent for Applicant submitted that several of these documents do not constitute prior art and the remaining are not material anticipatory prior art.

Annexure IX is Indian National Phase Patent Appl. No.: 00698/KOLNP/2005 titled 'Dioxolane thymine and combinations for use against resistant strains of HIV.' This corresponds to US provisional application 60/431,812 having priority date of 9 December 2002. The International publication date is 24 June 2004. Since this date falls after the claimed priority of the present application of 14 January 2003, this document is not a valid prior art.

Annexure XI is US Patent No. 7,094,413 titled 'Combination therapy for treatment of HIV infection' (Buelow et al, granted on 22 August 2006). This patent is also not a valid prior art since the date of publication (1 July 2004) is significantly after the claimed priority date of the present application (14 January 2003).

Annexure XII is the proceeding from The 12th Conference on Retroviruses and Opportunistic Infections, The Body Cover: The Complete HIV/AIDS

Resource titled 'No difference seen in resistance profiles of emtricitabine and lamivudine'. This is also not a valid prior art as this article is published on February 25, 2005.

Annexure X is US Patent No. 6,194,391 titled '3'-azido-2',3'-dideoxyundme administration to treat HIV and related test protocol' (Schinazi et al, granted on 27 February 2001). This patent discloses a method and composition for treating HIV in humans by administering 3'-azido-2',3'-dideoxyundme (CS-87) in combination with other anti-HIV drug selected from indinavir, nelfinavir, [FTI], dd4FC, abacavir, adefovir, PMPA, efavirenz, etc. The subject matter of present invention is different from the present invention as present invention provides a co-formulation of tenofovir and emtricitabine as active ingredients and does not include CS-87.

Annexure XIII is US Patent No. 4,808,716 titled '9-(phosphonylmethoxyalkyl)adenines, the method of preparation and utilization thereof' (Hoi et al, granted on 28 February 1989). This relates to 9-(phosphonylmethoxyalkyl)adenine (tenofovir) as well as their preparation and utilization. These compounds exhibit biological effects (e.g. antiviral) or can be converted into compounds with such effects. This citation does not teach formulation of tenofovir and emtricitabine and is not an art of the present invention.

Annexure XIV is US Patent No. 5,922,695 titled 'Antiviral phosphonmethoxy nucleotide analogs having increased oral bioavailability' (Arimilli et al, granted on 13 July 1999). This patent teaches the novel compounds that comprise esters of antiviral phosphonmethoxy nucleotide analogs with carbonates and/or carbamates. These compounds are useful as intermediates for the preparation of antiviral compounds or oligonucleotides, or are useful for efficient oral delivery of such analogs directly to patients for antiviral therapy or prophylaxis. This patent does not teach or suggest the formulation of tenofovir and emtricitabine claimed in the present

invention

Annexure XV is US Patent No 5,047,407 titled '2-substituted-5-substituted-1,3-oxathiolanes with antiviral properties' (Bcilleau et al, Granted on 10 September 1991). This patent relates to compositions comprising novel substituted 1,3-oxathiolane cyclic compounds having pharmacological activity for preventing or treating HIV infections in mammals and their method of preparation. The subject matter of this patent is different from the present invention as this patent document does suggest or disclose any co-formulation of TDF and FTC and carrier.

Annexure XVI is US Patent No 5,210,085 titled 'Method for the synthesis, compositions and use of 2'-deoxy-5-fluoro-3'thiacytidine and related compounds' (Liotta et al, granted on 11 May 1993). This patent document relates to a method of preparing the antiviral compounds 2'-deoxy-5-fluoro-3'thiacytidine (emtricitabine, FTC) and various prodrug analogues of FTC and methods of using these compounds. Though this document teaches that FTC and its prodrug analogues are effective in the prevention and treatment of AIDS, it does not provide for its co-formulation with tenofovir.

Annexure XVII is US Patent No 5,204,466 titled 'Method and compositions for the synthesis of BCH-189 and related compounds' (Liotta et al, granted on 20 April 1993). This document relates to a method of preparing BCH-189 (2',3'-dideoxy-3'-thio-cytidine) predominantly its /i-isomer and its various analogs from inexpensive precursors with the option of introducing functionality as needed. No co formulation of FTC and TDF and carrier is disclosed or suggested in this patent document.

Annexure XVIII and Annexure XIX are the amended transmittal and final rejection of corresponding US application (Publication No. 2006/0246130 A1)

Ld. Agent for applicant submitted that each jurisdiction has its own standards of

patentability, and inventive step. It was submitted that in fact, Annexure XIX actually does not contain any finding of lack of novelty. The only rejections contained in such final rejection are based on 35 USC 103 and not lack of novelty.

Agent for Applicant reiterated that for a document to anticipate the claims of a patent specification, it must by itself disclose the same information as the claim in question. Mosaic of various documents is not permissible. Even otherwise it was submitted that the present application 3383/DELNP/2005) is novel over each of the cited document either alone or when taken together. The instant representation deserves to be rejected on this ground alone.

It is respectfully submitted that each and every averment of the representers under this ground is denied in toto. It is respectfully submitted that the onh documents relied on under this ground by the representers are

Indian Patent Application 698/KOLNP/2005 having an effective filing date of December 8, 2003 and priority date of December 9, 2002 The actual date of national phase entry of this citation is April 21, 2005;

Citations raised in the 1SR of the corresponding PCT International Application PCT/US2004/000832,

US Patent No. 6,194,391 (Schmazi et al)

US Patent No. 7,094,413 (Buelow ct al)

The Body Cover: The Complete HIV/AIDS Resource

US Patent No 4,808,716 (Hoi et al)

(g)US Patent No. 5,922,695 (Anmilli et al)

(h) US Patent No. 5,047,407 (Belleau et al)

(i) US Patent No. 5,210,085 (Liotta et al)

(j) US Patent No. 5,204,466 (Liotta et al)

At the outset, it is respectfully submitted that none of the above documents constitute prior art for the purpose of assessment of anticipation by prior

claiming for the following reasons

Section 25(1)(c) stipulates that an invention claimed in an Indian Patent Application is anticipated by prior claiming if it is claimed in a claim of a complete specification of published on or after the priority date of the applicants' claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicants' claim.

48 It is respectfully submitted that of none of the documents relied on by the representers, except for one, are for an Indian Patent application. It is therefore respectfully submitted that the following documents are immaterial for the purpose of assessment of anticipation by prior claiming.

Citations raised in the ISR of the corresponding PCT International Application PCT/US2004/000832,

US Patent No. 6,194,391 (Schmazi et al)

US Patent No. 7,094,413 (But-low et al)

The Body Cover- The Complete HIV/AIDS Resource

US Patent No. 4,808,716 (Hoi et al)

US Patent No. 5,922,695 (nmilh et al)

g. US Patent No. 5,047,407 (Belleau et al)

h. US Patent No. 5,210,085 (Liotta et al)

i. US Patent No. 5,204,466 (Liotta et al)

It is further submitted that to establish this ground, what is essential is that the cited Indian Patent Application must claim the exact invention being claimed in the opposed application. It is respectfully submitted that the one remaining document, namely Indian Patent Application 698/KOLNP/2005 does not claim a stable formulation comprising TDF and FTC and a binder.

It is respectfully submitted that Indian Patent Application 698/KOLNP/2005 relates to the use of Dioxolane thymine and combinations for use against

resistant strains of HIV. The said document does not claim a combination of TDF and FTC and earlier at all. On the contrary, the said document teaches that dioxolane thymine can be combined with other agents, which includes TDF, EFV, AZT, D4T, FTC etc. There is no claim in the said document which teaches a combination of TDF and FTC by themselves with an earlier as is claimed in the present invention.

It is therefore submitted that this ground of representation also deserves to be dismissed in toto.

To decide over the novelty or inventive step I need to analyze each document relied upon by the opponent and study revised 19 no's of claims submitted by the Agent for Applicant in view of them.

THE AMENDED CLAIM 1 RELATES TO:

"A pharmaceutical co-formulation comprising: (a) (2-(6-amino-purin-9-yl)-l-methylethoxymethyl]-phosphoric acid diisopropoxycarbonyloxymethyl ester. Fumarate (tenofovir disoproxil fumarate) and (2R, 5S, cis)-4-amino-5-fluoro-l-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine), (b) from 5% to 95% by weight of one or more pharmaceutically acceptable carriers and (c) the balance, if any, by one or more excipients."

Upon reading through the documents cited in ISR, I agree that:

D1 discloses the use of tenofovir disoproxil fumarate (TDF) in patients receiving lamivudine (3TC) or emtricitabine (FTC) (see page 1844, column 2, Second last paragraph). Although this document relates mainly to the treatment of the hepatitis B in HIV/HBV co-infected patients, it also reports that there was an anti-HIV activity (see page 1845, column 2, last paragraph before "Discussion").

D2 shows studies on the appearance of resistances in HIV when using tenofovir (PMPA) with 3TC or PMPA with FTC (see the passages mentioned in the search report).

D3 discloses that there is the intention of combining PMPA with FTC in a single pill

(see page 7, column 2, last paragraph).

D4 discloses the use of TDF in combination with 3TC for the treatment of HIV infections (see the passages mentioned in the search report).

D5 teaches that the combination of PMPA or adenovirus (PMEA) with 3TC induces an additive inhibition of the HIV replication in vitro.

D6 discloses the combination of FTC with PMEA for the treatment of hepatitis B. PMEA is mentioned in the description of the present patent application to be functional derivative of Tenofovir (see page 11, lines 15-18).

Indian Patent Application 698/KOLNP/2005 published on 24/02/2006 but claiming priority of US patent application no.60/431812 dated 09/12/2002 discloses the use of a dioxolane thymine compound for use in the treatment of HIV infections which exhibit resistance to 3TC and/or AZT. The compounds according to the present invention are combined with agents selected from (-)-FTC (Emtricitabine), Tenofovir (PMPA), EFV (Efavirenz), 3TC (Lamivudine), AZT (Zidovudine), ddI (Didanosine), ddC (Zalcitabine), Abacavir (ABC), D-D4FC (Reverset), D4T (Stavudine), Racivir, L-D4FC, NVP (Nevirapine), DLV (Delavirdine), SQVM (Saquinavir mesylate), RTV (Ritonavir), IDV (Indinavir), SQV (Saquinavir), NFV (Nelfinavir), APV (Amprenavir), LPV (Lopinavir), fuse on and mixtures thereof.

I also find that US Patent No. US 7,094,413 titled "COMBINATION THERAPY FOR TREATMENT OF HIV INFECTION", granted to Sangstat Medical Corporation and The Regents of the University Of California on 22/08/2006, claiming priority from US Patent Application No. 60/351,925 filed on 24/01/2002 The said US Patent discloses a method of treating an individual infected with HIV, comprising administering to an HIV infected individual a pharmaceutically effective amount of an immuno-modulatory peptide and at least one anti-retroviral agent chosen from Tenofovir and Emticitabine, amongst others.(**Annexure XI**) .

Annexure XII proceeding from The 12th Conference on Retroviruses and Opportunistic Infections, The Body Cover: The Complete HIV/AIDS

Resource titled 'No difference seen in resistance profiles of emtricitabine and lamivudine'. was published on February 25, 2005. Therefore this can not be considered valid prior art.

Annexure X is US Patent No 6,194,391 titled '3'-azido-2',3'-dideoxyundme administration to treat HIV and related test protocol' (Schinazi et al, granted on 27 February 2001). This patent discloses a method and composition for treating HIV in humans by administering 3'-azido-2',3'-dideoxyundme (CS-87) in combination with other anti-HIV drug selected from indinavir, nelfinavir, [FTI], dd4FC, abacavir, adefovir, PMPA, efavirenz, etc. The subject matter of present invention is different from the present invention as present invention provides a co-formulation of tenofovir and emtricitabine as active ingredients and does not include CS-87.

Annexure XIII is US Patent No. 4,808,716 titled '9-(phosphonylmethoxyalkyl)adenines, the method of preparation and utilization thereof (Hoi et al, granted on 28 February 1989). This relates to 9-(phosphonylmethoxyalkyl)adenine (tenofovir) as well as their preparation and utilization. These compounds exhibit biological effects (e.g. antiviral) or can be converted into compounds with such effects. This citation does not teach formulation of tenofovir and emtricitabine and is prior art of the present invention.

Annexure XIV is US Patent No 5,922,695 titled 'Antiviral phosphonmethoxy nucleotide analogs having increased oral bioavailability' (Arimilli et al, granted on 13 July 1999). This patent teaches the novel compounds that comprise esters of antiviral phosphonmethoxy nucleotide analogs with carbonates and/or carbamates. These compounds are useful as intermediates for the preparation of antiviral compounds or oligonucleotides, or are useful for efficient oral delivery of such analogs directly to patients for antiviral therapy or prophylaxis. This patent also does

not teach or suggest the formulation of tenofovir and emtricitabine claimed in the present invention

Annexure XV is US Patent No 5,047,407 titled '2-substituted-5-substituted-1,3-oxathiolanes with antiviral properties' (Belleau et al, Granted on 10 September 1991). This patent relates to compositions comprising novel substituted 1,3-oxathiolane cyclic compounds having pharmacological activity for preventing or treating HIV infections in mammals and their method of preparation. The subject matter of this patent is different from the present invention as this patent document does suggest or disclose any co-formulation of TDF and FTC and carrier.

Annexure XVI is US Patent No 5,210,085 titled 'Method for the synthesis, compositions and use of 2'-deoxy-5-fluoro-3-thiacytidine and related compounds' (Liotta et al, granted on 11 May 1993). This patent document relates to a method of preparing the antiviral compounds 2'-deoxy-5-fluoro-3-thiacytidine (emtricitabine, FTC) and various prodrug analogues of FTC and methods of using these compounds. Though this document teaches that FTC and its prodrug analogues are effective in the prevention and treatment of AIDS, it does not provide for its co-formulation with tenofovir.

Annexure XVII is US Patent No 5,204,466 titled 'Method and compositions for the synthesis of BCH-189 and related compounds' (Liotta et al, granted on 20 April 1993). This document relates to a method of preparing BCH-189 (2',3'-dideoxy-3'-thio-cytidine) predominantly its *i*-isomer and its various analogs from inexpensive precursors with the option of introducing functionality as needed. No co formulation of FTC and TDF and carrier is disclosed or suggested in this patent document.

Annexure XIX is the final rejection of corresponding US application (Publication No. 2006/0246130 A1) as being unpatentable over Liotta et al (WO

92/14743;09/03/92),Becker et al (WO 02/08241 A2;01/31/02) and Fiske et al (Pharmacokinetics,safety and tolerability of single escalating doses of DMP266,an HIV non-nucleoside reverse transcriptase inhibitor,in healthy volunteers,pharmaceutical research (New york) 1997,vol 14 no.11 suppl. Pp. S609.print.)

I agree to the contention of the Ld Agent for Applicant that each of the cited documents must individually and unambiguously reach every element of the claimed invention. Mosaicing or combining two documents is not permissible to establish lack of novelty.

It is quite evident that use of tenofovir disoproxil fumarate (TDF) in patients receiving lamivudine (3TC) or emtricitabine (FTC) for anti-HIV activity is well known in cited documents but pharmaceutical co-formulation with defined amount of 5 to 95 % carrier along with excipients has not been claimed.

Therefore, the subject-matter of these claims can be considered novel over documents over the cited documents.

Inventive Step

Opponent's submissions:

The alleged application does not meet the criteria of Inventive Step under Section 2(1)(ja) of the Patents Act, 1970 since, the subject-matter of claims 1-58 is obvious to a person skilled in the art and the invention does not involve any technical advancement as compared to the existing knowledge.

The alleged application lacks technical data showing that the problem posed in the prior art is solved by the present invention. Thus, the present application does not involve any technical advancement as compared to the existing knowledge known to a person skilled in the art.

The opponent brought to notice the US National Phase Application No.

2006/0246130 AI which has received a Final Rejection (**Annexure XIX**). As per **Annexure IV-B**, the US application has been finally rejected. It may be noted from **Annexure IV-C**, that the US specification is same as the Indian Specification under Opposition. Further, the arguments for rejection put forth by the US Patent Examiner (**Annexure XIX**) clearly and conclusively reject all conditions for patentability in the alleged inventions, under USPTO, as well as more strongly under Indian Patent Law

The Opponent submitted a copy of the International Preliminary Report on Patentability (Chapter II of the Patent Co-operation Treaty) (PCT Article 36 and Rule 70). The said copy is attached herewith as **Annexure VIII**.

The Opponent further submitted that there are additional prior arts in which the alleged invention has been disclosed other than those cited in Preliminary Examination Report to support the opposition. These prior arts in which the alleged invention is disclosed clearly shows that the said invention is not novel and lacking in inventive step. Thus, the alleged invention of the Applicant fails to meet Patentability Criteria under Section 2(1)(j), 2(1)(ja) of the Patent Act, 1970, as amended up to 2005. Additional Prior Art Patent Applications / Patents with priority dates preceding the priority date of the alleged patent application are listed as follows:

1. Indian National Phase Patent Application No: 00698/KOLNP/2005 A Title:

DIOXOLANE THYMINE AND COMBINATIONS FOR USE AGAINST
RESISTANT STRAINS OF HIV Priority Document No: US 60/431,812 Priority Date:
09/12/2002 Priority Country: U.S.A. Indian Filing Date: 21/04/2005 Indian Publication
Date: 24/02/2006

Applicant: THE UNIVERSITY OF GEORGIA RESEARCH FOUNDATION AND
EMORY UNIVERSITY

2. US Patent No.: 6,194,391

Title: 3'-AZIDO-2', 3'-DIDEOXYURIDINE ADMINISTRATION TO TREAT HIV
AND RELATED TEST PROTOCOL Priority Document No US 60/090,552 Priority
Date: 24/06/1998

Priority Country US

US Filing Date: 24/06/1999

Publication Date: 27/02/2001

Applicant: EMORY UNIVERSITY AND NORVIRIO
PHARMACEUTICALS LIMITED

3. US Patent No.- 7.094,413

Title: COMBINATION THERAPY FOR TREATMENT OF HIV
INFECTION

Priority Document No: US 60/351,925

Priority Date: 24/01/2002

Priority Country U.S.A

US Filing Date: 24/01/2003

Publication Date: 22/08/2006

Applicant: SANGSTAT MEDICAL CORPORATION AND THE
REGENTS OF THE UNIVERSITY OF CALIFORNIA

Applicant's Submissions :

The Agent for Applicant submitted that amended claims on this application now relate to a combination of TDF and FTC and carrier/excipients with high stability. They further submitted that different compositions and combinations of antiviral drugs are known in the prior art which contain different antiviral drugs. However, the chemical stability of such compositions and combinations is of concern as the individual component(s) can interact with each other or with the some external component thereby decreasing the efficacy and stability of the combination. The present application claims a stable pharmaceutical formulation of tenofovir disoproxil fumarate and emtricitabine with pharmaceutically acceptable carriers and excipients.

It was also submitted that none of the documents relied on by the representers actually teach or guide towards, either alone or in combination, towards the composition of the invention.

The Agent for Applicant further submitted that in paragraphs 8(ii)(b) and 8(ii)(b)(2), the Representers alleges that the present invention does not meet the criterion of inventive step under Section 2(1)(ja) of the Patents Act, 1970. The Representers rely on the same documents under this ground that they have relied on for the ground of lack of novelty, viz Annexures V to XIX. It is submitted that

inventive step or nonobviousness has to be judged by the standard of a person skilled in the art. The Representers have failed to file any expert evidence on the matter, thereby clearly admitting that for a person of skill in the art, the present invention is both inventive and non-obvious. It was further submitted that the entire¹ arguments of the representers under this ground are again either verbatim reproductions from the ISR, IPRP and Written Opinion of the corresponding PCT International Application or are mere statements regarding the title of other documents relied on. There is no detailed technical analysis of any of the

above documents to show how and why such documents can be combined. It was reiterated that even if this were done, ex post facto, it would not teach or suggest the composition of the present invention.

It was submitted that in the art it is known to combine various antiviral drugs. However, none of the citations relied on by the representers teach a combination of TDF and FTC to arrive at a stable formulation where a eutectic mixture of the two is not formed, thereby ensuring greater self stability, and greater control over dosage regimens. In fact, the said documents when combined actually teach away from using TDF and FTC as a formulation. For example, D2 (Murry et al., Journal of Virology, 77, 2003: 1120-30) teaches that the methionine-to-valine mutation in codon 184 (M184V) in reverse transcriptase (RT) of human immunodeficiency virus type 1 (HIV-1) or simian immunodeficiency virus (SIV) confers resistance to lamivudine and increases the sensitivity to tenofovir. Variants resistant to both drugs are found to have the lysine-to-arginine mutation at codon 65 (K65R), which has previously been associated with resistance to PMPA in both SIV and HIV. The document further states that although the addition of PMPA to the FTC therapy induces a decrease in the virus loads in plasma, these loads eventually return to pre-PMPA levels in each case. All animals receiving this combination develop the K65R

mutation. These results demonstrate that the combination of PMPA with 3TC or (-)-FTC selects for the K65R mutation and against the M184V mutation in SIV RT.

It was further submitted that chemical stability of TDF and FTC is of concern due to their low pKa values of 3.75 and 2.65, respectively TDF is subject to hydrolytic deamination of the exocyclic amine of the adenine nucleobase, and to hydrolysis of one or both of the POC ester groups. TDF not only is a labile ester, it also is the salt with fumaric acid, an organic diacid. Only one carboxyl group of the fumaric acid is consumed for salt formation, the remaining carboxyl would have been expected (in a combination product) to be free to catalyze hydrolytic deamination of 5-fluoro cytosine nucleobase of FTC to form 5-fluoro uridine nucleobase. The acid-catalyzed deamination of FTC forms ammonia, which in turn would have been expected to catalyze the hydrolytic degradation of TDF to mono-POC PMPA (mono-ester of TDF), formaldehyde, isopropanol and carbonic acid. The carbonic acid would have been expected to further degrade the FTC, thereby creating more ammonia. The formaldehyde also would have been expected to cross-link FTC to produce dimers. The result of all this was that one could have expected a substantial prospect of reciprocal catalytic degradation. They further submitted that the prior art actually teaches that since a combination of TDF and FTC is at risk of catalytic hydrolysis, a person skilled in the art would have been prevented from considering a combination of TDF and FTC. It would not have been obvious to attempt to formulate TDF and FTC in the same dosage form which is claimed in the present invention. Thus, the present invention is clearly inventive over the cited prior art.

I once again reproduce my findings in the various prior art documents as follows: D1 discloses the use of tenofovir disoproxil fumarate (TDF) in patients receiving lamivudine (3TC) or emtricitabine (FTC) (see page 1844, column 2, Second last paragraph). Although this document relates mainly to the treatment of the hepatitis B in

HIV/HBV co-infected patients, it also reports that there was an anti-HIV activity (see page 1845, column 2, last paragraph before "Discussion").

D2 shows studies on the appearance of resistances in SIV when using tenofovir (PMPA) with 3TC or PMPA with FTC (see the passages mentioned in the search report).

D3 discloses that there is the intention of combining PMPA with FTC in a single pill (see page 7, column 2, last paragraph).

D4 discloses the use of TDF in combination with 3TC for the treatment of HIV infections (see the passages mentioned in the search report).

D5 teaches that the combination of PMPA or adenovirus (PMEA) with 3TC induces an additive inhibition of the HIV replication in vitro.

D6 discloses the combination of FTC with PMEA for the treatment of hepatitis B. PMEA is mentioned in the description of the present patent application to be functional derivative of Tenofovir (see page 11, lines 15-18).

Indian Patent Application 698/KOLNP/2005 published on 24/02/2006 but claiming priority of US patent application no.60/431812 dated 09/12/2002 discloses the use of a dioxolane thymine compound for use in the treatment of HIV infections which exhibit resistance to 3TC and/or AZT. The compounds according to the present invention are combined with agents selected from (-)-FTC (Emtricitabine), Tenofovir (PMPA), EFV (Efavirenz), 3TC (Lamivudine), AZT (Zidovudine), ddI (Didanosine), ddC (Zalcitabine), Abacavir (ABC), D-D4FC (Reverset), D4T (Stavudine), Racivir, L-D4FC, NVP (Nevirapine), DLV (Delavirdine), SQVM (Saquinavir mesylate), RTV (Ritonavir), IDV (Indinavir), SQV (Saquinavir), NFV (Nelfinavir), APV (Amprenavir), LPV (Lopinavir), fuse on and mixtures thereof.

I also find that US Patent No. US 7,094,413 titled "COMBINATION THERAPY FOR TREATMENT OF HIV INFECTION", granted to Sangstat Medical Corporation and The

Regents of the University Of California on 22/08/2006, claiming priority from US Patent Application No. 60/351,925 filed on 24/01/2002 The said US Patent discloses a method of treating an individual infected with HIV, comprising administering to an HIV infected individual a pharmaceutically effective amount of an immuno-modulatory peptide and at least one anti-retroviral agent chosen from Tenofovir and Emticitabine, amongst others.(**Annexure XI**) .

Annexure XII proceeding from The 12th Conference on Retroviruses and Opportunistic Infections, The Body Cover: The Complete HIV/AIDS Resource titled 'No difference seen in resistance profiles of emtricitabine and lamivudine'. was published on February 25, 2005. Therefore this can not be considered valid prior art.

Annexure X is US Patent No 6,194,391 titled '3'-azido-2',3'-dideoxyundme administration to treat HIV and related test protocol' (Schinazi et al, granted on 27 February 2001). This patent discloses a method and composition for treating HIV in humans by administering 3'-azido-2',3'-dideoxyundme (CS-87) in combination with other anti-HIV drug selected from indinavir, nelfinavir, [FTI], dd4FC, abacavir, adefovir, PMPA, efavirenz, etc. The subject matter of present invention is different from the present invention as present invention provides a co-formulation of tenofovir and emtncitabme as active ingredients and does not include CS-87.

Annexure XIII is US Patent No. 4,808,716 titled '9-(phosphonylmethoxyalkyl)adcnincs, die method of preparation and utilization thereof (Hoi et al, granted on 28 February 1989). This relates to ne\ 9-(phosphonylmethoxyalkyl)adenme (tenofovir) as well as their preparation and utilization. These compounds exhibit biological effects (e.g. antiviral) or can be converted into compounds with such effects. This citation does not teach formulation of tenofovir and emtricitabme and earner of the present invention.

Annexure XIV is US Patent No 5,922,695 titled 'Antiviral phosphonmethoxy

nucleotide analogs having increased oral bioavailability' (Arimilli et al, granted on 13 July 1999). This patent teaches the novel compounds that comprise esters of antiviral phosphonmethoxy nucleotide analogs with carbonates and/or carbamates. These compounds are useful as intermediates for the preparation of antiviral compounds or oligonucleotides, or are useful for efficient oral delivery of such analogs directly to patients for antiviral therapy or prophylaxis. This patent also does not teach or suggest the formulation of tenofovir and emtricitabine claimed in the present invention

Annexure XV is US Patent No 5,047,407 titled '2-substituted-5-substituted-1,3-oxathiolanes with antiviral properties' (Belleau et al, Granted on 10 September 1991). This patent relates to compositions comprising novel substituted 1,3-oxathiolane cyclic compounds having pharmacological activity for preventing or treating HIV infections in mammals and their method of preparation. The subject matter of this patent is different from the present invention as this patent document does suggest or disclose any co-formulation of TDF and FTC and carrier.

Annexure XVI is US Patent No 5,210,085 titled 'Method for the synthesis, compositions and use of 2'-deoxy-5-fluoro-3-thiacytidine and related compounds' (Liotta et al, granted on 11 May 1993). This patent document relates to a method of preparing the antiviral compounds 2'-deoxy-5-fluoro-3-thiacytidine (emtricitabine, FTC) and various prodrug analogues of FTC and methods of using these compounds. Though this document teaches that FTC

and its prodrug analogues are effective in the prevention and treatment of AIDS, it does not provide for its co-formulation with tenofovir.

Annexure XVII is US Patent No 5,204,466 titled 'Method and compositions for the synthesis of BCH-189 and related compounds' (Liotta et al, granted on 20 April 1993). This document relates to a method of preparing BCH-189 (2',3'-dideoxy-3'-thio-cytidine) predominantly its /i-isomer and its various analogs from inexpensive precursors with the option of introducing functionality as needed. No co formulation of FTC and TDF and carrier is disclosed or suggested in this patent document.

Annexure XIX is the final rejection of corresponding US application (Publication No. 2006/0246130 A1) as being unpatentable over Liotta et al (WO 92/14743;09/03/92),Becker et al (WO 02/08241 A2;01/31/02) and Fiske et al (Pharmacokinetics,safety and tolerability of single escalating doses of DMP266,an HIVnon-nucleoside reverse transcriptase inhibitor,in healthy volunteers,pharmaceutical research (New york) 1997,vol 14 no.11 suppl. Pp. S609.print.)

The amended claims of this application relates to a pharmaceutical formulation of tenofovir disoproxil fumarate and emtricitabine with pharmaceutically acceptable carriers and excipients.

I find that tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) are well known in the prior art documents as above for the treatment of the hepatitis B in HIV/HBV co-infected patients and their anti-HIV activity. Further carriers and excipients used are also well known.

I conclude that amended claims 19 no's does not meet the criteria of Inventive Step under Section 2(1)(ja) of the Patents Act, 1970 since, the subject-matter of 19 no's claims is obvious to a person skilled in the art as this shall be obvious to prepare a

pharmaceutical formulation of known tenofovir disoproxil fumarate and emtricitabine with known pharmaceutically acceptable carriers and excipients.

I also draw my conclusion from the US National Phase Application No. 2006/0246130 A1 which has received a Final Rejection (**Annexure XIX**). As per **Annexure IV-B**, the US application has been finally rejected and as per **Annexure IV-C**, that the US specification is same as the Indian Specification under Opposition. Further, the arguments for rejection put forth by the US Patent Examiner (**Annexure XIX**) clearly and conclusively reject patentability of the alleged invention under USPTO and whereas patentability condition is more stringent under Indian Patent Law.

I also cannot over rule International Preliminary Report on Patentability (Chapter II of the Patent Co-operation Treaty) (PCT Article 36 and Rule 70). (**Annexure VIII**).

The alleged application lacks technical data to show technical advancement as compared to the existing knowledge or having economic significance to make the invention not obvious to a person skilled in the art. There is nothing before me to prove enhanced efficacy or higher stability of the composition as submitted by the Agent for Applicant. There for in the absence of the same an inventive step cannot be established.

Not patentable invention U/S 3(d)

Opponent's submissions:

The Opponent submitted that the alleged invention clearly falls within the scope of Section 3(d) of The Patents Act, 1970. They said that Section 3(d) of the Indian Patent Act, unequivocally states 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 is not patentable. The explanation of Section 3(d) also clarifies that the isomers, salts, combinations and other derivatives of known substance shall be considered as the same substance, unless they differ significantly in properties with regard to efficacy.

The Agent for Opponent further quoted from the report of The Body where it has been unambiguously stated:

"Lamivudine (3TC, Epivir) and Emtricitabine (FTC, Emtriva) are extremely similar drugs

In /act, Emtricitabine is Lamivudine with one fluorine in one of the rings of the product

To the surprise of nobody, only minimal differences were found between the resistance profile of either drug. What this means, in practical terms, for patients is that emtricitabine and lamivudine are really interchangeable.

When a study whose main goal was to show differences between 2 products ends in a statement like "It is unclear that any of these differences were clinically significant," it simply means that there is no difference in the "resistance profile of these products" (Annexures XII).

Therefore, it is submitted by the Opponent that the alleged invention be barred from obtaining a Patent in India as it fails to discharge the onerous burden imposed upon it by Section 3(d) of The Patents Act, 1970.

The specification clearly admits the fact that the active ingredients as well as the compositions are obvious in the light of various prior disclosures relating to patent/ patent applications made in the alleged specification. These individual components have been in public domain prior to 01.01.1995 and hence, are not patentable in India, singly or in combination as per Section 3(d) The Patents act, 1970.

Applicant's submissions:

Agent for Applicant submitted that full evidence of improvements in properties relating to efficacy have been submitted in the specification. In addition, it is further submitted that the representers have failed to show exactly why Section 3(d) is attracted in the present application. They further submitted that this defect in the representation is incurable and is also an evidence of the fact that the entire representation is mala fide and vexatious.

I strongly take cognizance of the statements in the specification at page 36 that the combinations of the inventions may be tested for in vitro activity against HIV and sensitivity, and for cytotoxicity in laboratory adapted cell lines, e.g. MT2 and in peripheral blood mononuclear cells (PBMC) according to standard assays developed for testing

anti-HIV compounds, such as WO02/068058 and US 647541. It means that inventors are not sure about the efficacy of this pharmaceutical composition. I do not find any technical data in the submissions made by Agent for Applicant or in the specification, which can establish enhancement of the efficacy of this combination of known constituents. I agree to the contention of the Agent for opponent that specification has not demonstrated any significant therapeutic efficacy of the composition

I conclude from my above findings that the pharmaceutical composition or co-formulation or oral pharmaceutical dosage form in the form of tablet of same as claimed in amended claims of the Patent Application no. 3383/DELNP/2005, do not qualify the test of patentability under section 3(d) of the Patent Act 1970. Therefore, Applicant is denied patent on the amended claims as there is nothing before me to prove efficacy of the claimed pharmaceutical co-formulation.

Alleged invention is mere admixture

Opponent's submissions:

It was submitted by the Agent for Opponent that the application for the alleged invention is fatally affected by the provisions of Section 3(e) of The Patents Act, 1970. They further stated that the subject matter of the alleged specification is nothing but a mere admixture, which only results in the aggregation of their properties.

The invention of the alleged patent application is a mere admixture of known substances as disclosed in the preceding as well as in the following prior arts. In the light of the prior arts, the alleged invention is a simple admixture, merely resulting in the aggregation of properties.

The alleged application also clearly admits the fact, "*that combinations of compounds can give rise to increased cytotoxicity*" (page 2, line 25-26).

US Patent No. 4,808,716 for Tenofovir was first granted to Ceskoslovenska Akademie ved on February 28, 1989. The invention titled "9-(phosphonylmethoxyalkyl) adenines (Tenofovir), the method of preparation and utilization thereof, has foreign priority from CS Application No. 3017-85 filed on Apr 25, 1985. (**Annexure XIII**) .

In 1991, Gilead Sciences, Inc. and the Czech academic institution signed a license to allow Gilead to market Tenofovir. In 1996, in vivo antiviral activity of TDF was demonstrated. Gilead developed a salt of Tenofovir (disoproxil fumarate), and received a patent for this formulation in 1999. The said US Patent No. 5,922,695 titled "Antiviral phosphonmethoxy nucleotide analogs having increased oral bioavailability" granted to Gilead Sciences, Inc. on July 13, 1999, having priority from U.S. Provisional Patent Application Serial No. 60/022,708, filed July 26, 1996. (**Annexure XIV**).

US Patent No. 5,047,407 titled "2-substituted-5-substituted-1, 3-oxathiolanes with antiviral properties" for Lamivudine was first granted to IAF BioChem International, Inc on September 10, 1991 and has priority from US Application No. US308101 filed on Feb. 8, 1989 and CA Application No. CA2152269 filed on Dec. 21, 1992. (**Annexure XV**).

US Patent No. 5,210,085 for Emtricitabine was first granted to Emory University on May 11, 1993. The invention titled "Method for the synthesis, compositions and use of 2'-deoxy-5-fluoro-3¹-thiacytidine and related compounds", has priority from US Application No. 07/473,318 filed on Feb. 1, 1990. (**Annexure XVI**).

US Patent No. 5,204,466 for BCH-189 (3TC or Lamivudine is one of the two components of BCH-189) titled "Method and compositions for the synthesis of BCH-189 and related compounds" was granted to Emory University on April 20, 1993. (**Annexure XVII**).

All the three components of the alleged invention are patented prior to 01.01.1995. The alleged invention is a combination of patented compounds, which are not patentable for product patents in India .The alleged combination, is therefore not patentable in India.

Applicant's Submissions:

Agent for Applicant submitted that the representers have made hasty and incorrect reading of the present application and claims. It was submitted that the claimed combination of TD1* and FTC and carrier provides tremendous stability by control over formation of a eutectic mixture of TDF and FTC, thereby enabling greater control over dosage regimen. They further submitted that this is one of the

advantages of the invention which is evidence of synergy and that a clear reading of the complete specification would clearly establish every evidence of synergy. Unexpected enhanced stability of pharmaceutical formulation of the present invention provides for an improved property as compared to the properties of the individual ingredients. The pharmaceutical acceptable carrier included in the formulation prevent the formation of eutectic mixture of TDF and FTC. The eutectic mixture has lower melting point and thus is amorphous and not as stable as the original individual crystal forms of the starting materials. Thus, increased stability of the formulation by incorporation of the carrier makes the formulation a synergistic formulation and not a mere admixture of the active ingredients Thus, this ground does not hold relevance for the present application.

The representers refer to the line of the specification which states that "that combination of compounds can give rise to increased cytotoxicity". They submitted that the written description clearly goes ahead to state on page 2, lines 26-28 that 'AZT and recombinant interferon-a have an increased cytotoxic effect on normal human bone marrow recombinant cells.' They submitted that the representers have not proceeded beyond reading of the background of the invention in their haste to oppose this application.

It is beyond doubt that active ingredients tenofovir disoproxil fumarate and emtricitabine of the pharmaceutical co-formulation are well known in prior arts and the acceptable carriers/excipients are not novel.

I do not find any concrete technical data which can establish about the pharmaceutical co-formulation comprising: (a) (2-(6-amino-purin-9-yl)-1-methylethoxymethyl]-phosphoric acid diisopropoxycarbonyloxymethyl ester. Fumarate (tenofovir disoproxil fumarate) and (2R, 5S, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine), (b) from 5% to 95% by weight of one or more pharmaceutically acceptable

carriers and (c) the balance, if any, by one or more excipients of synergistic effect which goes beyond sum total of individual active ingredients.

I find that the complete specification do speak about the chemical stability of the claimed pharmaceutical composition. I also find the definition of word “synergy” in the specification. I also read through the submission of Agent for Applicant that combination of TD1* and FTC and carrier provides tremendous stability by control over formation of a eutectic mixture of TDF and FTC, thereby enabling greater control over dosage regimen.

I do not find any comparative technical data to show synergistic effect of the pharmaceutical co-formulation or to prove control over formation of eutectic mixture affecting chemical stability; in absence of which they seems to mere statements.

Therefore in absence of any comparative technical data to show synergistic effect, I conclude that the claimed pharmaceutical co-formulation is mere admixture of known ingredients and is not patentable under section 3(e).

Publicly Known or Used

Opponent’s Submissions:

The Opponent submitted that the application for grant of Patent filed by the Applicant deserves to be rejected on the ground that the invention claimed by the Applicant in their Complete Specification was publicly known/ used in India and elsewhere before the priority date of the claim of the Applicant. Therefore, the application deserves to be rejected under Section 25 (1) (c) of The Patents Act, 1970.

The Opponent submitted that the combination of Tenofovir (Tenofovir Disoproxil Fumarate, Tenofovir DF, TDF), Emtricitabine (-(-)FTC), Lamivudine (3TC), Efavirenz and combinations thereof are extensively manufactured, used and marketed in India. They provided the list of Tenofovir, Emtricitabine, Lamivudine.

Efavirenz and combinations thereof, manufactured, used and marketed in India.

The alleged composition and components of the alleged compositions are prior used in India, extensively. No patent for combinations of known prior patented (patented prior to 01.01.1995) molecules may be granted as per Section 3(d) of The Patents Act, 1970.

Applicant's Submissions:

Agent for Applicant submitted that the averments of the representers have no basis as to establish the ground of prior public use, it is necessary for an representer to show the exact date of use and such date must be prior to the priority date of the opposed application.

They submitted that representers have not studied their case thoroughly and have drafted their representation in a hurry. The first paragraph of paragraph 9(c) states that "the application for grant of patent filed by the Applicant deserves to be rejected on the ground that the invention claimed by the Applicant in their Complete Specification was publicly known/used in India and elsewhere before the priority date of the claim of the Applicant. Therefore, the application deserves to be rejected under Section 25(1)(c) of The Patents Act, 1970. The ground of opposition of publicly known/used is covered in Section 25(1)(d) and not in Section 25(1)(c).

They also submitted that the representers have not submitted evidence that any of the formulations listed by them in paragraph 9(c) were actually used before the priority date of the instant application. That in any event, none of the formulations actually correspond to the formulation of the present invention, namely a combination of TDF and FTC and carrier.

The only additional submission of the representers that it is not permissible to "patent combinations of known prior patented molecules under Section 3(d)" is

meaningless in the context of the ground of anticipation by prior public use.

Therefore, submitted that the representers have failed to establish this ground of opposition which deserves to be dismissed in toto.

I do not find from the documentary evidences submitted by the Agent for opponent that the claimed pharmaceutical co-formulation comprising: (a) (2-(6-amino-purin-9-yl)-1-methylethoxymethyl]-phosphoric acid diisopropoxycarbonyloxymethyl ester. Fumarate (tenofovir disoproxil fumarate) and (2R, 5S, cis)-4-amino-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one (emtricitabine), (b) from 5% to 95% by weight of one or more pharmaceutically acceptable carriers and (c) the balance, if any, by one or more excipients is exactly in prior public use.

Based upon my finding above, this ground of opposition is hereby dismissed.

I do not find worth discussing other grounds of opposition as submissions of both parties on those have no impact on outcome of the case now.

In view of above findings and facts on records, I refuse to grant patent on this patent application no. **3383/DELNP/2005** on the ground of lack of inventive step section 25(e) read with section 2(1)(ja) and not patentable invention under section 25(f) read with section 3(d)&3(e).

This application is disposed with no cost to either party.

Dated this 25th. day of March, 2009

N R Meena
Asstt. Controller of Patents & Designs

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