

March 13<sup>th</sup>, 2014

The Controller of Patents  
The Patent Office  
Intellectual Property Office Building,  
Plot No. 32, Sector 14, Dwarka,  
New Delhi-110075, India

Re: Representation u/s 25(1) of the Patents Act -  
in Indian Patent Application No. 6087/DELNP/2005 filed on 27<sup>th</sup> December, 2005.  
National Phase of PCT Application No. PCT/US2004/012472 claiming priority from the  
US Patent Application No. 60/474,368 dated 03<sup>rd</sup> May 2003.  
Applicant: Pharmasset, Inc  
Representation filed by: **Natco Pharma Limited.**  
Our Ref: **OPP0075**

Dear Sirs,

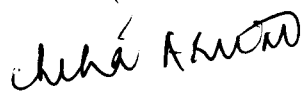
We submit herewith a Representation u/s 25(1) of the Patents Act, 2005, along with evidence available with us, Form 7A is also submitted along with.

We crave leave of the Controller to submit additional documents or evidence or if necessary to support any of the averments in the representation as may be necessitated in the proceeding.

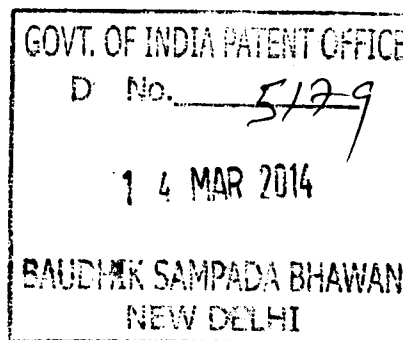
The Controller is requested to take the documents on record and proceed further in the matter and keep the petitioner advised of each and every step taken in the matter.

Lastly, we request the Controller to grant us an opportunity of being heard before the above representation is finally decided.

Thanking you,

  
CHITRA ARVIND  
FOR RAJESHWARI & ASSOCIATES  
AGENT FOR THE OPPONENT

**Encl:** Form 7A in triplicate  
Opposition in triplicate  
List of documents and documents in triplicate



ORIGINAL

14 MAR 2014

6087 DELNP 05

FORM 7A  
THE PATENTS ACT, 1970 (39 OF 1970)  
AND  
THE PATENTS RULES, 2003  
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT  
[See Rule 55]

We Natco Pharma Limited. Natco House, Road No.2, Banjara Hills, Hyderabad 500033, India hereby give representation by way of opposition to the grant of patent in respect of application No: 6087/DELNP/2005 dated 27<sup>th</sup> December 2005 made by Pharmasset Inc. Delaware, 303A, College Road East, Princeton New Jersey 08540, United States of America and published on 9th May 2005 on the grounds:

- i. **Section 25(1)(b)/(c):** Lack of novelty
- ii. **Section 25(1)(e):** Lack of inventive step
- iii. **Section 25(1)(f):** Subject of claims 1 to 20 is not an invention within the meaning of this Act or is not patentable under this Act
- iv. **Section 25(1)g:** The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
- v. **Section 25(1)h:** The Applicant has failed to disclose to the Controller the information required under Section 8.

Our address for service in India is:

CHITRA ARVIND  
RAJESHWARI & ASSOCIATES  
AMSOFT BUSINESS CENTRE  
UNITECH TRADE CENTRE  
Sector 43, Gurgaon- 122 002.  
Haryana, India.  
Tel: +91-11-41038911;  
Fax: +91-11-43851067  
Mobile No. 9910048684

Dated, this 14<sup>th</sup> day of March, 2014.

*Chitra Arvind*

CHITRA ARVIND  
of Rajeshwari & Associates  
Agent for the Opponent

To  
The Controller of Patents,  
The Patent Office, Delhi

ORIGINAL

6087 DELNP 05

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI 4 MAR 2014

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

AND

IN THE MATTER OF:

Indian Patent Application **6087/DELNP/2005** filed on 27<sup>th</sup> December 2005 claiming priority from the US Patent Application No. 60/474,368 dated 3<sup>rd</sup> May 2003, by Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472 (Published as WO 2005/003147).

AND

IN THE MATTER OF:

Natco Pharma Limited.

...PETITIONER/OPPONENT

VS.

Pharmasset, Inc.

...RESPONDENTS/APPLICANTS

**PRE-GRANT OPPOSITION BY NATCO PHARMA LIMITED.**

Sl. No.	PARTICULARS	Page Nos.
1.	Representation u/s 25(1) by the Petitioner/Opponent	1-27
2.	Annexure 1: Copy of claims of 6087/DELNP/2005 filed on 18.03.2010	28-31
3.	Annexure 2: Copy of WO2001/92282.	32-333
4.	Annexure 3: Copy of WO2001/90121.	334-629
5.	Annexure 4: Copy of WO2002/057425.	630-864
6.	Annexure 5: Copy of WO1990/01036.	865-893
7.	Annexure 6: Copy of WO1999/43691.	894-1002
8.	Annexure 7: Copy of WO2002/18404.	1003-1228
9.	Annexure 8: Copy of WO2002/32920.	1229-1458

ORIGINAL

6007 DELHI 05

14 MAR 2014

10.	Annexure 9: Copy of Article Perlman et al.	1459-1466
11.	Annexure 10: Copy of Article Schinazi et al.	1467-1474
12.	Power of Attorney in our favour.	(to follow)

Dated this 13<sup>th</sup> day of March, 2014.

*Chitra Arvind*

CHITRA ARVIND  
FOR RAJESHWARI & ASSOCIATES  
AGENT FOR THE OPPONENT

To,  
The Controller of Patents  
The Patent Office, Delhi

6087-05

ORIGINAL  
14 MAR 2014

**BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE,  
DELHI**

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES  
2003.

IN THE MATTER OF a pre-grant representation under Section 25(1)

**AND**

IN THE MATTER OF:

Indian Patent Application **6087/DELNP/2005** filed on 27<sup>th</sup> December 2005 claiming  
priority from the US Patent Application No. 60/474,368 dated 3<sup>rd</sup> May 2003, by  
Pharmasset, Inc. National Phase of PCT Application No. PCT/US2004/012472  
(Published as WO 2005/003147).

**AND**

IN THE MATTER OF:

Natco Pharma Limited.  
Natco House, Road No.2,  
Banjara Hills,  
Hyderabad 500033,  
India.

...PETITIONER/OPPONENT

VS.

PHARMASSET, INC.

A Corporation organized and existing under and by virtue of the laws of the state of  
Delaware.

303A, College Road East,  
Princeton New Jersey 08540,  
United States of America.

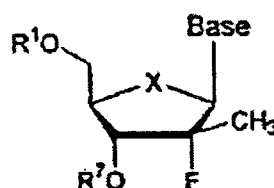
...RESPONDENTS/APPLICANTS

**STATEMENT OF CASE OF OPPONENT**

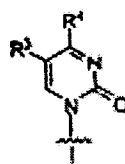
1. The Petitioner/Opponent has learnt that the Applicant has filed an Indian  
National Phase Application No. 6087/DELNP/2005, which is currently  
pending before the Patent Office. The said patent application is entitled "A  
(2'R)-2'-Deoxy-2'-Fluoro-2'-C-Methyl Nucleoside" and is drawn to a set of  
chemical compounds represented by a common structure, encompassing  
several millions of compounds, known as a Markush structure. The said

application being the impugned application claims priority from U.S. Provisional Application No. 60/474,368 filed on May 03, 2003. The said Indian Application is the National Phase Entry of the PCT publication WO 2005/003147 filed on April 21, 2004. The Indian Application was filed on 27<sup>th</sup> December, 2005. The Application was initially filed with 131 claims, which apparently appear to have been amended by way of Form 13 filed on or about 30<sup>th</sup> March, 2012, amending the claims to 20 in number. The Request for Examination vide Form 18 has been filed on 26.05.2006. The examination report has been issued by the Indian Patent Office on 18<sup>th</sup> February 2009, the response for the same is filed on 17<sup>th</sup> March 2010. The claims as filed on 18.03.2010 and on record are as below and annexed herewith as Annexure 1:

1. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside ( $\beta$ -D or  $\beta$ -L) or its pharmaceutically acceptable salt of the structure:

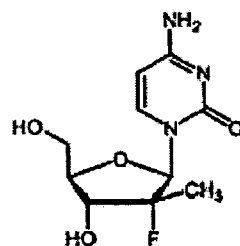


wherein the Base is a pyrimidine base represented by the following formula



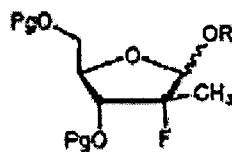
X is O; R1 and R7 are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, a C1-C10 alkyl, a C1-C10 alkyl sulfonyl, a phenyl C1-C10 alkyl sulfonyl, a biphenyl C1-C10 alkyl sulfonyl, or a naphthyl C1-C10 alkyl sulfonyl; and R3 is H and R4 is NH2 or OH.

2. The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside ( $\beta$ -D or  $\beta$ -L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R7 is H and R1 is a monophosphate, a diphosphate, or a triphosphate.
3. The (2'R)-2'-deoxy-2',-fluoro-2'-C-methyl nucleoside ( $\beta$ -D) as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R7 is H and R1 is a diphosphate or a triphosphate.
4. The (2'R)-2'-deoxy-2'-fiuoro-2'-C-methyl nucleoside ( $\beta$ -D or  $\beta$ -L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R7 is H and R1 is a triphosphate.
5. The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R1 and R7 are H.
6. A (2'R)-2'-deoxy-2'-fiuoro-2'-C-methyl nucleoside ( $\beta$ -D) or its pharmaceutically acceptable salt thereof of the formula:



7. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
8. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 2 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 3 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
10. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 4 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
11. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 5 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
12. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 6 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
13. A method of synthesizing the nucleoside as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:

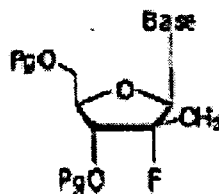


I-4

wherein R is C1-C4 lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C1-C10 alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH<sub>2</sub>-C1-C10 alkyl, CH<sub>2</sub>-C1-C10 alkenyl, CH<sub>2</sub>-phenyl, CH<sub>2</sub>-biphenyl, CH<sub>2</sub>-naphthyl, CH<sub>2</sub>O-C1-C10 alkyl, CH<sub>2</sub>O-phenyl, CH<sub>2</sub>O-biphenyl, CH<sub>2</sub>O-naphthyl, SO<sub>2</sub>-C1-C10 alkyl, SO<sub>2</sub>-phenyl, SO<sub>2</sub>-biphenyl, SO<sub>2</sub>-naphthyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or

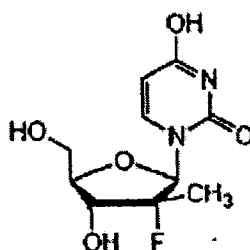
both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

14. A method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting a 3'-OPg or a 5'-OPg of a compound having the following structure:



wherein, each Pg is independently a protecting group selected from among C(O)-C1-C10 alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH3, CH2-C1-C10 alkyl, CH2-C1-C10 alkenyl, CH2-phenyl, CH2-biphenyl, CH2-naphthyl, CH2O-C1-C10 alkyl, CH2Ophenyl, CH2O-biphenyl, CH2O-naphthyl, SO2-C1-C10 alkyl, SO2-phenyl, SO2-biphenyl, SO2-naphthyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

15. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside ( $\beta$ -D) or its pharmaceutically acceptable salt thereof of the formula:



16. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 15 or its pharmaceutically acceptable salt and optionally a pharmaceutically acceptable carrier.

17. A liposomal composition comprising liposomes comprising about 50 mg to about 2000 mg or more of the compound as claimed in claim 1 and optionally a pharmaceutically acceptable carrier.
18. A liposomal composition comprising liposomes comprising about 50 mg to about 2000 mg or more of the compound as claimed in claim 6 and optionally a pharmaceutically acceptable carrier.
19. A liposomal composition comprising liposomes comprising about 50 mg to about 2000 mg or more of the compound as claimed in claim 15 and optionally a pharmaceutically acceptable carrier.
20. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside ( $\beta$ -D or  $\beta$ -L) or its pharmaceutically acceptable salt substantially as herein described with reference to the accompanying drawings and as illustrated in the foregoing examples.

2. The claims currently on record, may be summarized as below:

Claim 1 of the present application being the impugned application is drawn to common structure, encompassing several millions of compounds, known as a Markush structure. The markush structure pertains to a modified nucleoside. Claims 2, 3, 4 and 5, are drawn to various embodiments of the modified nucleoside as disclosed at Claim 1 along with their pharmaceutically acceptable salt. Claim 6, is drawn to a compound represented by chemical structure and its pharmaceutically acceptable salts. Claim 7, is drawn to a composition comprising a compound encompassed in claim 1 and as their pharmaceutically acceptable salt and along with the carrier. Claim 8, is drawn to a composition comprising the compound of claim 2 and pharmaceutically acceptable salt and carrier. Claim 9 to 12 are drawn to a composition

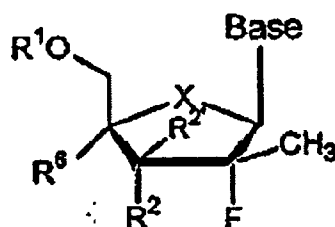
comprising compound as claimed in claim 2-5 as their salts along with pharmaceutically acceptable carrier. Claim 13 and 14, are drawn to a process for preparing the compound as disclosed at Claim 1. Claim 15, is drawn to a compound represented by a chemical structure and its pharmaceutically acceptable salt which is not supported by the disclosure in the specification. Claim 16, is drawn to the composition comprising a compound of claim 15 and its pharmaceutically acceptable salt or carrier. Again it is to be noted that subject matter of Claim 15 and Claim 16 are not disclosed anywhere in the specification of impugned application. Claim 17 to 19, are drawn to the liposomal composition comprising compound as claimed in claim 1, claim 6 and claim 15 along with their pharmaceutically acceptable carrier. Claim 20 is an omnibus claim, which is not allowable and tenable under this act.

Without acquiescing to the admissibility of such claims both in terms of technicality and procedural aspects, the opponent proceeds to submit the grounds of opposition pertaining to the said claims on record.

3. Before traversing the various grounds of the opposition, the Opponent proceeds to analyze the disclosure in the impugned application. The impugned patent application is purported to be drawn from US priority 60/474,368. The present application, being the impugned application appears to be drawn to modified nucleoside as inhibitors of RNA dependent viral replication. In the background art, the impugned specification discloses that Hepatitis C virus (HCV) infection is a major infection and that both pestivirus and hepacivirus belongs to the Flaviviridae family of viruses. The specification discloses that various inhibitors such as protease inhibitor, helicase inhibitors, nucleotide polymerase inhibitor, etc are already known for the treatment of HCV. The

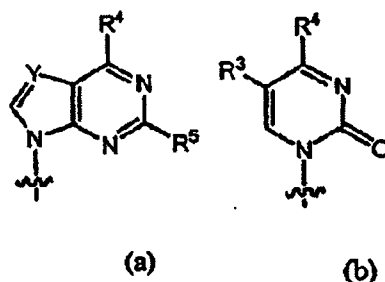
impugned specification admits that branched nucleosides for the treatment of flavivirus and pestivirus are already known and that such drugs are reported to have toxicity problems. The impugned specification also admits that the 2'-methyl nucleosides and 2'-fluoro nucleosides and such type of structures are already known for the treatment of flaviviruses (including HCV) and pestiviruses. The present specification is merely drawn to compounds that are nothing but the modification of already known nucleoside derivatives as per the applicants own admission in the impugned specification.

The impugned specification appears to drawn to compounds and its pharmaceutically salts or prodrugs, depicted by a chemical structure, encompassing several millions of compounds, known as a Markush structure. The structure is represented herebelow at Figure 1.



**Figure 1:** Chemical structure of the impugned specification

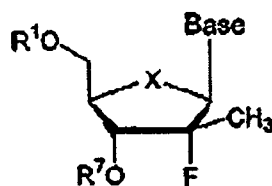
The specification then proceeds to provide various substitutions as possible embodiments represented generally by  $R^1$ ,  $R^2$ ,  $R^{2'}$ ,  $R^6$ ,  $X$  and Base. In the general chemical structure of the specification represented at Figure 1 herein for ready reference, the nitrogenous base may be any of naturally occurring or modified purine or pyrimidine base and may be any of a and b as depicted in Figure 2.



**Figure 2: Structure of Bases**

From the above figure, it appears that substituted thymine, uracil, adenine, guanine and cytosine base may also be arrived from the structures represented at Figure 2 (a) and (b) by suitable substitutions of various embodiments disclosed.

In addition, the impugned specification discloses another set of chemical compounds depicted by chemical structure, encompassing several millions of compounds, known as a Markush structure. The structure is represented herebelow at Figure 3.



**Figure 3: The chemical structure of impugned specification**

The specification then proceeds to provide various possible substitutions represented by  $R^1$ ,  $R^2$ ,  $R^{2'}$ ,  $R^6$ , X and Base. In the general, chemical structure represented at Figure 3, the nitrogenous base may be any of naturally occurring or modified purine or pyrimidine or other base as encompassed in structure.

The impugned specification further proceeds to list the phosphate ester derivatives of the compound of chemical structure of Figure 1 and Figure 3.

It may be noted that several million compounds are encompassed within the said structures, however in the examples a mere handful of compounds appear to be enumerated.

The application also provides various general disclosures pertaining to dosage, compositions, administrations and use of the said compounds of this impugned specification and that these compounds may be co-administered with other known antiviral compounds. It may be noted that the impugned specification does not appear to exemplify any pharmaceutical compositions, however the applicant proceeds to claim compositions comprising compounds.

The process for preparation of these compounds is provided as a general process which is purportedly applicable to the million of compounds encompassed in the said general chemical structure and even such a process is admitted as prior art process. It may be noted that the two processes as provided by the impugned specification appears does not specifically disclose the changes to be made to the experimental conditions for each substructure. In other words, the impugned specification purports that the various classes of compounds that are disclosed in the impugned application all may be arrived at by the two disclosed procedures, which are incomplete as such.

Examples 1 and 2 appear to be drawn to a general synthetic procedure for preparation of 2'-dexoy-2'-fluoro-2'-C-methylcytidine. Example 3 and 4 purportedly discloses a general procedure for preparation of 2'-dexoy-2'-fluoro-2'-C-methylpurine more specifically 2'-dexoy-2'-fluoro-2'-C-methyladenosine. Example 5 appear to be drawn to the antiviral activity of 2'-dexoy-2'-fluoro-2'-C-methylcytidine. The impugned specification does not

provide any experimental conditions for the process of performing the experiments. More importantly it is to be noted that the impugned specification does not provide any analytical data demonstrating that the compounds of the application were actually synthesized and in possession by the Applicant before the filing of the application. It is submitted that all compounds that are not claimed ought to be considered as disclaimed. The opponent further submit the claims as amended and currently on record are not patentable under this act on various grounds as below:

### **GROUND I**

#### **I) Section 25(1)(b)/(c): Lack of novelty**

The invention as claimed in Claims 1-20 lacks novelty and are not patentable under Section 25(1)(b)(c) of the Patents Act, 1970 (as amended in 2005; hereinafter referred to as "the Act"). It is submitted that none of the claims of **6087/DELNP/2005** are novel and they are all liable to be rejected on this ground alone.

It is submitted that all claims 1 to 20 of the impugned patent application are anticipated by disclosure in WO2001/92282 (hereinafter referred as WO'282) and annexed herewith as Annexure-2. WO'282 by Novirio Pharmaceuticals Limited and Universita Degli Studi Di Cagliari has been published on 06<sup>th</sup> December, 2001, prior to the priority date of the impugned application. It is submitted that the compounds as claimed in Claims 1 to 6 and claim 15 are known and encompassed within the basic chemical structure of the WO'282 application.

Before discussing this ground of opposition, the various chemical parts of the chemical structure claimed in Claim 1 are discussed. The set of chemical

compounds as represented by general structure claimed in claim 1 and the compound of claim 6 and claim 15 comprises of a nitrogenous base which is attached to a sugar molecule. The 2' position of the sugar molecule is substituted by a fluoro and a methyl group and 3' position of the sugar is substituted by a hydroxyl group.

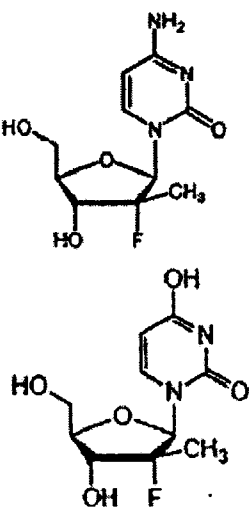
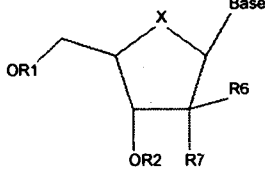
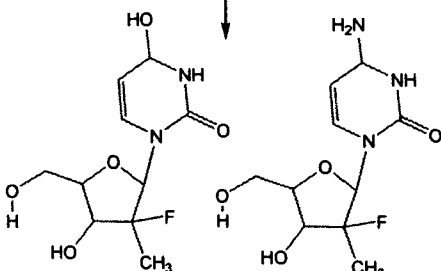
It is submitted that most of these components are common to all antiviral compounds generally used for a treatment of HIV infections, HCV infections and the like. *Prima facie* it is submitted that the said compound for treatment of HIV and/or HCV infections are nothing but a mere extension of other HIV and HCV compounds already known and established in prior art. This is an admitted position by the applicants in their impugned application.

WO'282 discloses a basic chemical structure encompassing several thousand compounds for treating viral infections caused by flavivirus and pestivirus.

The basic structure of WO'282 is also drawn to a sugar attached to a nitrogenous base. Further, WO'282 discloses various substituents which encompass in its structure several possible nucleosides. The various embodiments of WO'282 includes Markush Structure at formula XI, XVI, XVII and XVIII. All these formulas provide various options for substitutions. The substitutions discloses that the nitrogenous base may be a purine or a pyrimidine, further several options are provided for the substitution of R1, R6, R7, R9 and R10. From these substitutions it is clear that WO'282 envisages and encompasses compounds similar to the compounds of the impugned patent application. The compounds of WO'282, comprises a fluoro and a methyl substitution at the 2'-position and a hydroxyl group at the 3'-position

of the sugar molecule. It is submitted that the compound of the impugned application may be arrived by substitution of various substituents in the general markush structure of WO'282. The same is illustrated at Table 1. Various examples of WO'282 may be examined and found to fall within the scope of the impugned specification and vice versa.

**Table 1:** Comparison of structure of Impugned Patent Application and WO'282

Impugned Patent Application (6087/DELNP/2005)	WO2001/92282
	 <p>Base= Purine or Pyrimidine;  R1, R2= Phosphate Prodrug, Monophosphate, Diphosphate or Triphosphate, Hydrogen, Acyl, Alkyl, etc;  X= O, S, SO2 or CH2;  R6= Fluoro, H, OH, alkyl, Cl, Br, I, NH2, etc;  R7= Alkyl (including lower alkyl), H, Hydroxy, Azido, Cyano, Chloro, Bromo, Iodo, NH2, etc;</p> <p>On substituting the above substituents</p>  <p>Disclosed as Structure XI, XVI, XVII and XVIII, Page- 9, 11 to 13; Claim-8, 10, 11, 12, 35, 37 to 39, 59, 61-63, 86, 88-90, 110 and 112-114.</p>

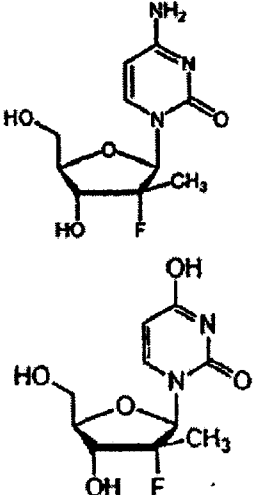
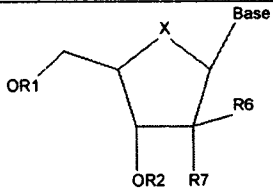
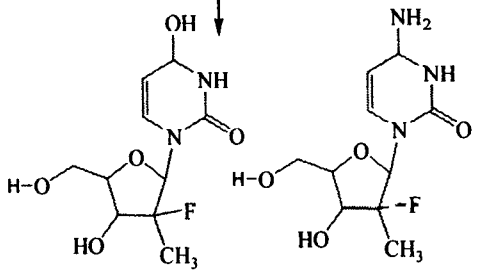
In the alternate and without prejudice to the above, it is submitted that all claims 1 to 20 of the impugned patent application are anticipated by disclosure in WO2001/90121 (hereinafter referred as WO'121) and annexed herewith as Annexure-3. WO'121 by Novirio Pharmaceuticals Limited and Universita

Degli Studi Di Cagliari has been published on 29<sup>th</sup> November, 2001, prior to the priority date of the impugned application. It is submitted that the set of chemical compounds as represented by general structure claimed in claim 1 and the compound of claim 6 and claim 15 are known and encompassed within the basic chemical structure of WO'121 application.

WO'121 discloses a chemical structure encompassing several thousand compounds for treating viral infections.

The basic structure of WO'121 is drawn to a sugar attached to a nitrogenous base. Further, WO'121 discloses various substituents which encompasses in its markush several possible nucleosides. The various embodiments of WO'121 includes basic chemical structure at formula XI, XVI, XVII and XVIII. The structure at these formulas provides various options for substitutions. The substitutions disclose that the base may be a purine or a pyrimidine, further several options are provided for the substitution of R1, R6, R7, R9 and R10. From these substitutions it is clear that WO'121 envisages and encompasses compounds same as the compounds of the impugned patent application. The compounds of WO'121, comprises a halo and an alkyl substitution in the 2'-position and hydroxyl group at the 3'-position of the sugar molecule. It is submitted that the compound of the present application being the impugned application may be arrived by substitution of various substituent of WO'121. The same is illustrated at Table 2. Various examples of WO'121 may be examined and found to fall within the scope of the impugned specification and vice versa.

**Table 2:** Comparison of structure of Impugned Patent Application and WO'121

Impugned Patent Application (6087/DELNP/2005)	WO2001/90121
	 <p>Base= Purine or Pyrimidine;  R1, R2= Phosphate Prodrug, Monophosphate, Diphosphate or Triphosphate, Hydrogen, Acyl, Alkyl, etc;  X= O, S, SO<sub>2</sub> or CH<sub>2</sub>;  R6= Fluoro, H, OH, alkyl, Cl, Br, I, NH<sub>2</sub>, etc;  R7= Alkyl (including lower alkyl), H, Hydroxy, Azido, Cyano, Chloro, Bromo, Iodo, NH<sub>2</sub>, etc;</p> <p>On substituting the above substituents</p>  <p>Disclosed as Structure XI, XVI, XVII and XVIII, Page- 13-16, 29, 33, 40, 45; Claim-8, 10-12, 35, 37-39, 59, 61-63, 86 and 88-90.</p>

In the alternate and without prejudice to the above, it is submitted that all claims 1 to 20 of the impugned patent application are anticipated by disclosure in WO2002/057425 (hereinafter referred as WO'425) and annexed herewith as Annexure-4. WO'425 by Merck & Co. has been published on 25<sup>th</sup> July, 2002, prior to the priority date of the impugned application. It is submitted that the compounds as claimed in Claims 1 to 6 and claim 15 are known and encompassed within the basic chemical structure of the WO'425 application.

Before discussing this ground of opposition, the various chemical parts or components of the general chemical structure as disclosed in Claim 1 are analysed. The set of chemical compounds as represented by general structure claimed in claim 1 and the compound of claim 6 and claim 15 comprises of a nitrogenous base which is attached to a sugar molecule. The 2' position of the sugar molecule is substituted by a fluoro and a methyl group and 3' position of the sugar is substituted by a hydroxyl group.

It is submitted that all these components are common to all antiviral compounds generally used for a treatment of HIV infections, HCV infections and the like. *Prima facie* it is submitted that the said compound for treatment of HIV and/or HCV infections are nothing but a mere extension of other HIV and HCV compounds already known and established in prior art. This is an admitted position by the applicants in their impugned application.

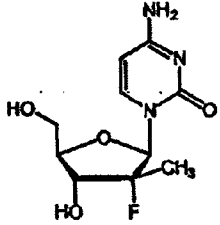
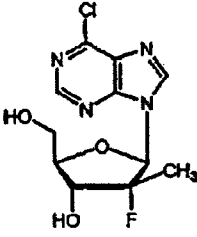
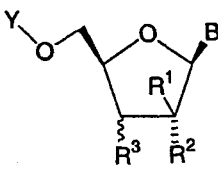
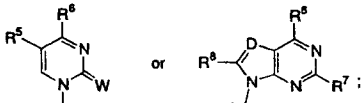
WO'425 discloses a basic chemical structure encompassing several thousand of compounds for treating RNA dependent viral infections.

The basic structure of WO'425 is also drawn to a sugar attached to a nitrogenous base. Further, WO'425 discloses various substituents which encompasses in its general structure several thousands of compounds. The various embodiments of WO'425 includes Markush Structure at formula I, II and III. Formula III provides various options for substitutions. As per the various embodiments disclosed in WO'425 it can be clearly seen that WO'425 discloses a nitrogenous base which may be selected from a group of compounds which appears to be the derivatives of purine or a pyrimidine, further several options are provided for the substitution of R1, R2, R3 and Y.

From these substitutions it is clear that WO'425 envisages and encompasses compounds similar to the compounds of the impugned patent application. The compounds of WO'425, also discloses a fluoro and an alkyl substitution in the 2' position and a hydroxyl group at 3' position of sugar molecule. The base is selected from the compounds represented by the general structure which appears to be the purine or pyrimidine derivatives. It is submitted that the compounds of the impugned application may be arrived by substitution of various substituents of WO'425. Various examples of WO'425 may be examined and found to fall within the scope of the impugned specification and vice versa.

For instance, example 1 and 3 of the impugned specification may be obtained by substituting various embodiments in the markush structure of WO'425. The same is illustrated at Table 3.

**Table 3:** Comparison of Examples of Impugned Patent Application and markush of WO'425

Impugned Patent Application (6087/DELNP/2005)	WO2002/057425
<p>Example-1:</p>  <p>Example-3:</p> 	<p>Disclosed as Formula III, Page- 17, and Claim-5 and claim-6</p>  <p>(III)</p> <p>R<sup>1</sup> is hydrogen, CF<sub>3</sub>, or C<sub>1-4</sub> alkyl and one of R<sup>2</sup> and R<sup>3</sup> is OH or C<sub>1-4</sub> alkoxy and the other of R<sup>2</sup> and R<sup>3</sup> is selected from the group consisting of hydrogen, hydroxy, fluoro,</p>  <p>B is</p> <p>Y is H, C<sub>1-10</sub> alkylcarbonyl, P<sub>3</sub>O<sub>9</sub>H<sub>4</sub>, P<sub>2</sub>O<sub>6</sub>H<sub>3</sub>, or P(O)R<sup>9</sup>R<sup>10</sup>;</p>

Thus it is submitted that all compounds of WO'425 fall within the purview of the markush of the impugned application and the compounds of the impugned application are encompassed within the markush structure of WO'425.

Therefore, the markush and all compounds encompassed within the markush are anticipated by disclosure in WO'425.

It is submitted that all claims 1 to 20 are anticipated by disclosure in prior art by an individual reading of either WO'282 or WO'121 or WO'425.

Thus, all claims 1 to 20 ought to be rejected on this ground only.

## GROUND II

### II) Section 25(1)(e): Lack of inventive step

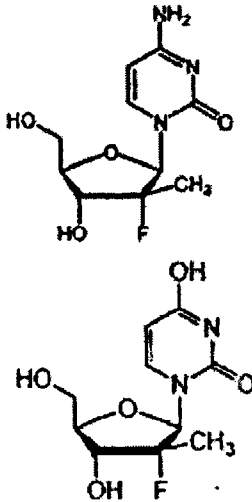
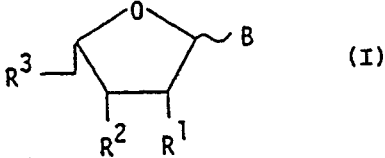
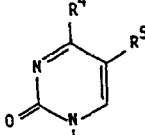
The invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the claim.

It is submitted that compounds of chemically similar structures are known and well established in prior art for their use as antiviral agents.

For instance, WO1990/01036, published on 08.02.1990 (also published as EP0352248, published on 24.01.1990) hereinafter referred as WO'036 and annexed herewith as Annexure-5 discloses the L-ribofuranosyl nucleoside analogues used for the treatment of infections caused by HIV virus, hepatitis B virus or herpes virus. The nucleoside analogues are represented by a common structure known as markush structure. For ease of illustration the compounds

claimed in the claims of impugned application are compared with the general markush of WO'036 herebelow in Table 4.

**Table 4:** Comparison of structure of Impugned Patent Application and WO'036

Impugned Patent Application (6087/DELNP/2005)	WO1990/01036
	 (I) $R^1: \text{H, F}$ $R^2: \text{H, OH, F, N}_3, \text{CN}$ $R^3: \text{OH}$ B is adenine, guanine, hypoxanthine, 2,6-diaminopurine  or $R^4: \text{OH, NH}_2;$ $R^5: \text{H, CH}_3, \text{C}_2\text{H}_5$ Discloses at Page-4, Line-1 to Page-5; Claim-1 and Claim-7

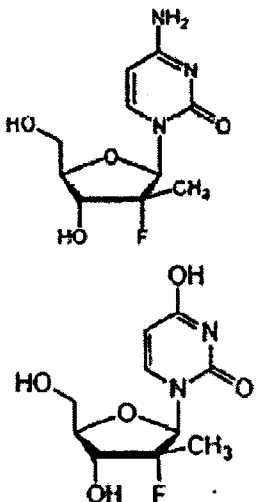
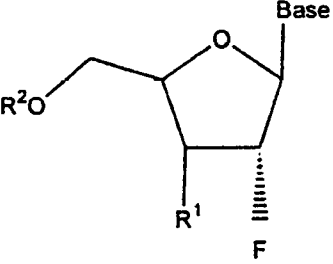
The compounds disclosed by WO'036 comprises of a sugar molecule attached to the nitrogenous base wherein, the sugar molecule is substituted at 2'-position with the fluoro group and 3'-position is substituted with hydroxyl group. The compounds of WO'036 are disclosed as being effective for the treatment of HIV, HBV infection. Thus from above Table-4, it can be seen that on substituting the above markush with various substituents, the compounds thus obtained are similar to the compounds disclosed by the impugned application.

WO 1999/43691, hereinafter WO'691 and annexed herewith as Annexure-6 discloses masked 2'-Fluoronucleoside analogues and their therapeutic use in

the treatment of HBV, HCV, HIV infection and abnormal cell proliferation such as tumors and cancer.

The compounds as disclosed by WO'691 comprise of a nucleoside i.e. a nitrogenous base with sugar molecule. These compounds are chemically similar to the general structure of the impugned application as disclosed at Claim 1.

**Table 5:** Chemical similarity of compounds claimed at Claim 6 and 15 of the impugned application with that of WO'691

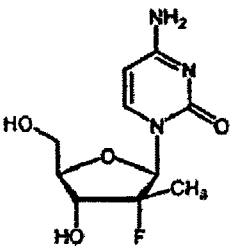
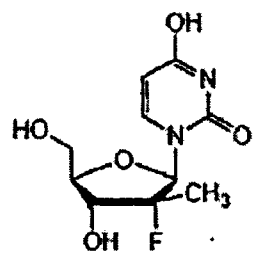
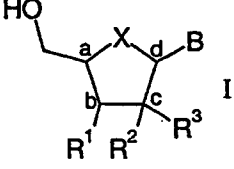
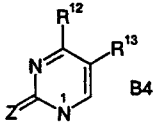
Impugned Patent Application (6087/DELNP/2005)	WO 1999/43691
	<p data-bbox="842 920 1406 1064">Discloses at Page-9, Line 20 to Page-10, Line-9; Page-10, Line-10 to 15; Page-14, Line - to 25; Claim-1, 6, 9, 10-13, 18, 21-24</p>  <p data-bbox="842 1339 1406 1440">Base is a purine or pyrimidine base as defined further herein; R<sup>1</sup> is OH, H, OR<sup>2</sup>, N<sub>3</sub>, CN, halogen, including F, or CF<sub>3</sub>, lower alkyl, R<sup>2</sup> is H, phosphate, including monophosphate, diphosphate, triphosphate.</p>

WO'691 is drawn to 2'-fluoronucleoside compound which are useful in the treatment of hepatitis infection, Hepatitis C infection and HIV infection and any abnormal cell proliferation.

WO2002/18404, published on 07.03.2002 hereinafter referred as WO'404 and annexed herewith as Annexure-7 also discloses structures which have antiviral activity. The compounds as disclosed in WO'404 are derivatives of nucleosides and comprises of a nitrogenous base with a sugar molecule. The compounds as disclosed in WO'404 are modified nucleosides wherein, the 2'

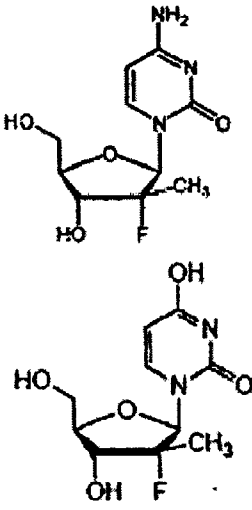
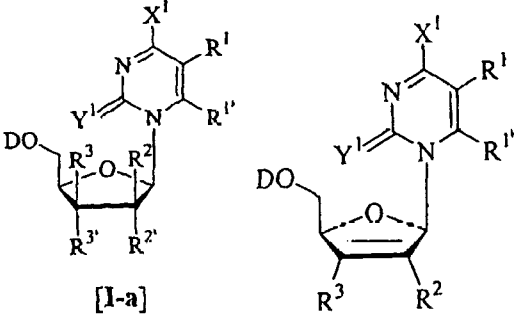
position of the sugar is substituted with either hydrogen or fluoro group. These compounds are also considered as active anti-viral compounds and are represented by the general formula as provided in the abstract of the specification. The chemical structures of WO'404 have the same components as that of the impugned application. The structures are compared at Table 6 for ready reference.

**Table 6:** Comparison of structure of Impugned Patent Application and WO'404

Impugned Patent Application (6087/DELNP/2005)	WO2002/18404
 	 <p><b>I</b></p> <p>R<sup>1</sup> is hydrogen, hydroxy, alkyl, hydroxyalkyl,  R<sup>2</sup> is hydrogen, hydroxy, alkoxy, chlorine, bromine or iodine;  R<sup>3</sup> is hydrogen;  R<sup>2</sup> and R<sup>3</sup> represent fluorine;  X is O, S or CH<sub>2</sub>;  B signifies a pyrimidine base B4 which is connected through the 1-nitrogen formula</p>  <p><b>B4</b></p> <p>Z is O or S;  R<sup>12</sup> is hydrogen, hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, aryl, aryloxy, heterocyclyl, heterocyclylamino, halogen, NR<sup>7</sup>R<sup>8</sup>, NHOR<sup>9</sup>, NHR<sup>7</sup>R<sup>8</sup> or  R<sup>13</sup> is hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, haloalkyl, cycloalkyl or  R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are as defined above; or</p> <p>(Disclosed at Page-2, Line-27 to Page-3, Line-7 and Page-4, Line-12 to Page-5, Line-4)</p>

WO2002/32920 hereinafter referred as WO'920 and annexed herewith as Annexure-8, published on 25.04.2002 before the priority date of impugned application. WO'920 discloses modified nucleosides represented by general structure for the treatment of viral infections and abnormal cellular proliferation. For ease of illustration, the compounds of the impugned application are compared with the compounds of WO'920 represented herebelow in Table 7.

**Table 7:** Comparison of structure of Impugned Patent Application and WO'920

Impugned Patent Application (6087/DELNP/2005)	WO2002/32920
	<p data-bbox="850 969 1396 1037">Disclosed at compound Ia, IIa, IIIa, Iva and XVIIIa</p> <div data-bbox="858 1048 1380 1361">  <p data-bbox="949 1328 1005 1361">[I-a]</p> </div> <p data-bbox="850 1373 1409 1451"><math>R^1</math> and <math>R^{1'}</math> is independently hydrogen, lower alkyl, each <math>R^2</math> and <math>R^{2'}</math> independently is hydrogen or halogen (F, Cl, Br or I), OH, SH, <math>OCH_3</math>, <math>SCH_3</math>, <math>NH_2</math>, <math>NHCH_3</math>, <math>CH=CH_2</math>, CN, <math>CH_2NH_2</math>, <math>CH_2OH</math>, <math>CO_2H</math>.</p> <p data-bbox="850 1462 1409 1518">Each <math>R^3</math> and <math>R^{3'}</math> independently is hydrogen or halogen (F, Cl, Br or I), OH, SH, D is hydrogen, alkyl,</p> <p data-bbox="850 1529 1409 1563"><math>X^1</math> and <math>X^2</math> is independently hydrogen, halogen (F, Cl, Br or I), <math>NH_2</math>, <math>Y^1</math> is O</p>

Thus it is well established that the compounds with nitrogenous base attached to a sugar molecule are known for antiviral activity. It is also established and admitted by the applicant that 2'-fluoro nucleosides are known for the treatment of hepatitis B, HCV and HIV infection. Moreover, it is again

admitted by the applicant that 2'-methyl nucleoside has been used for the treatment of infection caused by the flavivirus.

It is admitted that the modified nucleosides are already well established in prior art for their antiviral activity. For instance, Perlman et al (1985) annexed herewith as Annexure-9 discloses the antiviral activity of 2'-fluoro-5-substituted pyrimidine nucleosides wherein, the 2'-position of sugar molecule is substituted with a fluoro group and 3'-position is substituted with a hydroxyl group.

Also, Schinazi et al (2002) annexed herewith as Annexure-10 discloses such nucleoside analogs wherein the sugar molecules are attached at 2'-position with a fluoro group and 3'-position with hydroxyl group and the said compounds are known for anti-HIV activity.

Thus all claims 1-20 are obvious by a collective reading of prior art. The compounds of present invention are taught, suggested and motivated by disclosure in prior art. Hence, all claims are ought to be rejected on this ground only.

### GROUND III

**III) Section 25(1)(f): Subject of claims 1 to 20 is not an invention within the meaning of this Act or is not patentable under this Act**

a) The subject matter of claims 1-20 do not constitute an 'invention' as understood under Section 2(i)(j) of the Act:

It is submitted that since the claims 1-20 are not novel, not inventive and lack industrial application, they do not constitute an 'invention' under the Act.

- b) The subject matter of claims 1, 2, 3, 4, 5, 6 and 15 are not patentable under Section 3(d) of the Act:

The compounds of the impugned specification are nothing but derivatives of compounds known in prior art. This is an admitted position by the Applicants. The derivatives as disclosed in the impugned application also do not possess enhanced therapeutic efficacy over the closest compounds of prior art and therefore ought to be rejected on this ground only.

For instance, Example 5 is drawn to *in-vitro* assay of the compounds of the impugned patent application wherein, only the compound claimed in claim 6 is being compared with the unsubstituted nucleoside. Since, the compound of claim 6 is not compared with other compounds such compound should be disclaimed.

Claims 13 and 14 are drawn to a process for synthesis of the compounds as claimed in claim 1 and therefore these claims are drawn to a mere process without involving any new reactants or resultant products. Hence, these claims are ought to be rejected.

- c) The subject matter of claims 7, 8, 9, 10, 11, 12, 16, 17, 18 and 19 are not patentable under Section 3(e) of the Act:

These claims are drawn to a composition. The components of these composition do not act in a synergistic manner and hence these claims are ought to be rejected on this ground.

In regard, the Opponent craves leave to refer and rely on submission made in Grounds I-III above and the same are not being repeated for the sake of brevity.

**GROUND IV**

**IV) Section 25(1)g: The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.**

**A. Best Mode Not Disclosed:**

It is submitted that the complete specification does not sufficiently describe the invention and the method in which it is to be performed.

1. The specification discloses several thousands of compounds, but does not identify the most active compound. In absence of such identification, the best mode of performing the invention is not disclosed.

**B. Claims not supported by specification:**

1. Claim 15 is drawn to a chemical compound. Compound as claimed in this claim is not adequately described in the specification and also there is no exemplification of the said compound in the impugned application. Therefore, this claim is ought to be rejected.
2. The process as claimed in claim 13 and claim 14 is not clearly disclosed in the impugned application. The amended claims have been done mischievously and with malicious intent to introduce matter not being present in the impugned application. In absence of any support in the impugned patent application such claims should not be granted.

Hence, on this ground only all the claims are ought to be rejected.

**GROUND V**

- V.) Section 25(1)h: The Applicant has failed to disclose to the Controller the information required under Section 8.**

It is submitted that the Applicant/Respondent has failed to disclose the details of corresponding foreign applications filed, and on this ground alone the patent application should be rejected.

The Plaintiff filed patent applications in US with the same or substantially same inventions. Information regarding corresponding applications have not been disclosed to the Indian Patent Office. When the claims have a direct bearing and relationship with each other, failure to mention the non-disclosure of the filing of such corresponding or substantially same/ similar applications to the Patent Office amounts to gross suppression of material facts on which account the patent must be rejected.

**P R A Y E R**

In the fact and circumstances of the case, the Opponent prays as follows:

- i. that the Indian Patent Application No. 6087/DELNP/2005 made by PHARMASSET, INC., a corporation organized and existing under and by virtue of the laws of the state of Delaware. 303A, College Road East, Princeton New Jersey 08540, United States of America. be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;
- ii. the Opponent may be allowed to file further documents as evidence if necessary to support their averments;
- iii. the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;

- iv. the Opponent may be allowed to make further submissions in case the applicant makes any amendments in the claims;
- v. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this 13<sup>th</sup> day of March, 2014

*Chitra Arvind*

CHITRA ARVIND  
FOR RAJESHWARI & ASSOCIATES  
AGENT FOR THE OPPONENT