THE PATENTS ACT 1970

Section 25(1) read with Rule 55

IN THE MATTER OF:

Patent Application No. 6087/DELNP/2005

IN THE MATTER OF:

Pre-grant representations filed to the grant of patent under Section 25(1) of the Patents Act 1970 (as amended in 2005), and the patents rules 2005

GILEAD PHARMASSET LLC, USA; - **APPLICANT**

AND

1. OPTIMUS PHARMA LTD
2. INDIA CARES
3. SANKALP REHABILITATION TRUST
4. DELHI NETWORK OF POSITIVE PEOPLE (DNP+); AND THE INITIATIVE FOR MEDICINES, ACCESS & KNOWLEDGE, INC. (I-MAK) INC.
5. BDR PHARMACEUTICALS INTERNATIONAL PVT. LTD.

- OPPONENTS

Hearing held on 23rd, 24th and 25th February 2016

Present:

Mrs. Prathiba M. Singh (Senior Advocate), Mr. Sanjeev Kumar Tiwari, Mr. Amrish Tiwari, - Attorneys for the applicant

Mr. Anand Grover (Senior Advocate), Ms. Rameshwari - Attorneys for the Opponents Optimus Pharma Ltd., India Cares, and Sankalp Rehabilitation Trust

Mr. Md. Atiqullah - Examiner of Patents and Designs

Hearing held on 26th February, 2016

Present:

Mrs. Prathiba M. Singh (Senior Advocate), Mr. Sanjeev Kumar Tiwari, Mr. Amrish Tiwari, - Attorneys for the Applicant

Ms. Shwetasree Majumder - Attorneys for the Opponents DNP+ and IMAK

Mr. Md.Atiqullah - Examiner of Patents and Designs

Hearing held on 29th February, 2016

Present:

Mr. Sanjeev Kumar Tiwari, Mr. Amrish Tiwari,- Attorneys for the Applicant

Ms. Shwetasree Majumder - Attorney for the Opponent BDR Pharmaceuticals

Mr. Md.Atiqullah - Examiner of Patents and Designs

ORDER

1. Details and important dates of Application filed by GILEAD PHARMASSET, LLC. before IPO for grant of the Patent are mentioned herein below:

APPLICATION NUMBER	**6087/DELNP/2005**
APPLICANT NAME	**GILEAD PHARMASSET, LLC.**
DATE OF FILING	**27/12/2005**
PCT INTERNATIONAL Application no. & FILING DATE	**PCT/US2004/012472 Dated 21/04/2004**
PRIORITY Application no. &DATE	**US 60/1474368 Dated 30/05/2003**
TITLE OF INVENTION	**"A (2'R)-2'-DEOXY-2'FLUORO-2'-C-METHYL NUCLEOSIDE"**
Date of Request For Examination	**26/5/2006**
PUBLICATION DATE (U/S 11A)	**09/05/2008**
DATE OF FIRST EXAMINATION REPORT (FER)	**06/04/2009**
DATE OF RESPONSE TO FER	**18/03/2010**
HEARING NOTICE U/S 14 ISSUED ON	**07/05/2014**
HEARING U/S 14 HELD ON	**24/07/2014**

DECISION OF REFUSAL BY IPO	**13/01/2015**
REMANDED BACK BY Hon'ble DELHI HIGH COURT IN WRIT PETITION	**30/01/2015**
OPPOSITION FILED BY NATCO ON	**14/03/2014**
OPPOSITION FILED BY IMAK + DNP ON	**19/03/2014**
OPPOSITION FILED BY BDR PHARMA ON	**30/01/2015**
OPPOSITION FILED BY SANKALP ON	**30/01/2015**
OPPOSITION FILED BY OPTIMUS ON	**20/03/2015**
OPPOSITION FILED BY INDIA CARES ON	**23/06/2015**
NOTICE FOR OPPOSITIONS BY IPO FOR NATCO, DNP + IMAK, BDR, SANKALP, OPTIMUS.	**08/05/2015**
NOTICE FOR OPPOSITION BY IPO FOR INDIA CARES.	**31/07/2015**
RESPONSE FILED BY APPLICANT TO OPPOSITIONS - NATCO, DNP + IMAK, BDR, SANKALP, OPTIMUS	**07/08/2015**
RESPONSE FILED BY APPLICANT TO INDIA CARES	**30/10/2015**
OPPOSITION WITHDRAWAL LETTER FROM NATCO	**16/03/2015**
OPPOSITION HEARING NOTICES FOR DNP+ IMAK, BDR, SANKALP, OPTIMUS, INDIA CARES ISSUED ON	**18/01/2016**
ADDITIONAL DOCUMENTS FILED BY DNP+ IMAK TO RELY DURING PRE-GRANT OPPOSITION HEARING	**19/02/2016**
HEARING OF OPTIMUS, INDIA CARES, SANKALP, HELD ON	**23/02/2016** **24/02/2016** **25/02/2016**
HEARING OF DNP+ IMAK HELD ON	**26/02/2016**
HEARING OF BDR HELD ON	**29/02/2016**
WRITTEN NOTES OF ARGUMENTS FILED BY APPLICANT AND OPPONENTS - DNP+ IMAK, BDR, SANKALP, OPTIMUS, INDIA CARES ON	**11/03/2016 and 14/03/2016**

2. PRE GRANT OPPOSITIONS AND THEIR MAIN GROUNDS OF OPPOSITIONS:

I. OPTIMUS PHARMA LTD:

i. Section 25(1) (b) Lack of Novelty

ii. Section 25(1) (e) Lack of Inventive Step

iii. Section 25(1)(f) Subject of Claims 1-10 is not an invention and or is not patentable

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

II. SANKALP REHABILITATION TRUST

i. Section 25(1) (b) Lack of Novelty

ii. Section 25(1) (e) Lack of Inventive Step

iii. Section 25(1)(f) Subject of Claims 1-7 and 10 is not an invention and is/or are not patentable

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

III. INDIA CARES:

i. Section 25(1) (b) Lack of Novelty

ii. Section 25(1) (e) Lack of Inventive Step

iii. Section 25(1)(f) Subject of Claims 1-10 is not an invention and is/or are not patentable

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

IV. DNP+ and IMAK:

i. Section 25(1) (b) Lack of Novelty

ii. Section 25(1) (c) Invention has been published before the priority date of the claim

iii. Section 25(1) (e) Lack of Inventive Step

iv. Section 25(1)(f) Subject of Claims 1-10 is not an invention and is/or are not patentable

v. 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

vi. Section 25(1)(h) – The applicant has failed to disclose to the Controller the information required under Section 8

V. BDR PHARMACEUTICALS:

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 1-10 is not an invention and is/or are not patentable

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

3. During the oral hearings of Oppositions from February 23rd to February 29th, 2016 only three grounds of Oppositions were pressed by all the opponents i.e., OPTIMUS, INDIA CARES, SANKALP, DNP+ IMAK, BDR which are as below:

A. Section 25(1) (b) Lack of Novelty

B. Section 25(1) (e) Lack of Inventive Step; and

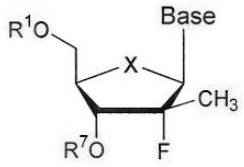
C. Section 25(1) (f) Not patentable under Section 3(d).

4. The Indian National Phase patent application was initially filed with 131 Claims. While complying with the objections of the FER under Section 21, the Applicant

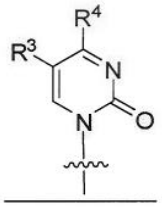
restricted the number of Claims 1 to 20 Claims. On August 07, 2015, in reply statement to pre-grant opposition under Rule 55(4), the Applicant amended Claims to total 16 Claims. The Applicant further amended claim on April, 29, 2016 to total 8 claims.

Currently pending Claims in the instant Application are as follows.

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



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



X is O; R^1 and R^7 are independently H, a monophosphate, a diphosphate, or a triphosphate;

R^3 is H and

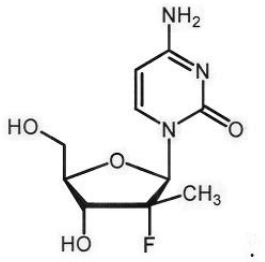
R^4 is NH_2 or OH.

2. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R^7 is H and R^1 is a monophosphate, diphosphate or a triphosphate.

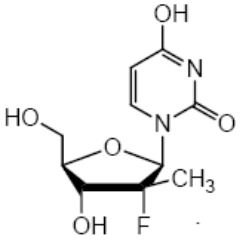
3. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R^7 is H and R^1 is a triphosphate.

4. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R^1 and R^7 are H.

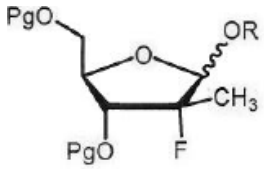
5. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) as claimed in claim 1 or its pharmaceutically acceptable salt thereof of the formula:



6. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D) as claimed in claim 1 or its pharmaceutically acceptable salt thereof of the formula:



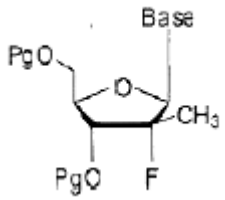
7. A method of synthesizing A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:



1-4

wherein R is C_1-C_4 lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C_1-C_{10} alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH_2-C_1-C_{10} alkyl, CH_2-C_1-C_{10} alkenyl, CH_2-phenyl, CH_2-biphenyl, CH_2-naphthyl, CH_2O-C_1-C_{10} alkyl, CH_2O-phenyl, CH_2O-biphenyl, CH_2O-naphthyl, SO_2-C_1-C_{10} alkyl, SO_2-phenyl, SO_2-biphenyl, SO_2-naphtyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

8. A method of synthesizing A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) 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)-C_1-C_{10} alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH_3, CH_2-C_1-C_{10} alkyl, CH_2-C_1-C_{10} alkenyl, CH_2-phenyl, CH_2-biphenyl, CH_2-naphthyl, CH_2O-C_1-C_{10} alkyl, CH_2O-phenyl, CH_2O-biphenyl, CH_2O-naphthyl, SO_2-C_1-C_{10} alkyl, SO_2-phenyl, SO_2-biphenyl, SO_2-naphtyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a l,3-(1,1,3,3-tetraisopropyldisiloxanylidene).

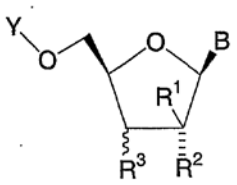
GROUNDS

SECTION 25(1) (B) LACK OF NOVELTY:

Arguments submitted by Opponents and Applicant w.r.t. lacks of Novelty are as below:

Submissions and arguments of Optimus, India Cares and Sankalp (combined together) on lack of Novelty/anticipation are as below:

5. All three Opponents relied only on WO 2002/057425 (WO'425) for lack of Novelty. Opponents relied on formula III of WO'425



(III)

Opponents argued that where multiple moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed, the substituted moieties, singly or plurally. Opponents submitted that the Applicant's allegation that fluorine is not specifically described is incorrect.

6. Opponents further submitted that the impugned invention has been disclosed in entirety and specifically points to the inhibition of the HCV NS5B site. It is also submitted that the compound disclosed in WO'425 Application is sterochemically specific and expressly claims the stereochemical configuration of the Fluorine in the 'down' position at the 2' position. Opponent argued that the invention of the Applicant is enabled in view of WO'425 and the prior knowledge, and a person skilled in the art would be able to perform the invention by resorting to fluorination at the 2'C position using DAST. Opponent argued that fluorinating agent in the art, such as DAST was routinely used to introduce fluorine moiety in primary, secondary and tertiary alcohols and following prior art documents were referred to in this regard.

a)Panckiewicz et al. (2000) - discloses Protection by Trityl Alcohol and deprotection by NaOH. From this, it can be inferred that the addition of fluorination can be done through a carefully controlled procedure.

b)Hayakawa et al. (1990) - Fluorination of nucleoside using DAST at 2' position with hydroxyl is disclosed and this prior art also depicts the inversion of configuration which happens as a result of use of DAST.

c)Wachtmeister et al. (1999) - discloses that fluorination of a tertiary alcohol a cyclopentanol compound with inversion of stereochemistry could be carried out with DAST.

d) R. P. Singh and J. M. Shreeve (2002) - This prior art discloses that fluorination of teritiary alcohols can be successfully achieved by using DAST and deoxoflour as reagents by a person skilled in the art.

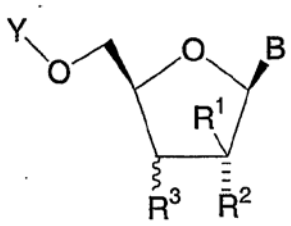
7. Opponents relied upon the judgment of Synthon BV vs. Smithkline Beecham [2005] UKHL 59, wherein the test of novelty entails two requirements: prior disclosure and enablement. In the said case it was held that the concepts of prior disclosure and enablement were incorrectly bundled together' as 'enabling disclosure' wherein the enablement was to be entirely derived from the anticipatory disclosure. The judgment further enunciated that, Anticipation was separated into two distinct requirements of disclosure and enablement with different standards and requirements. Hence, there is an unequivocal disjunction of the concept of 'enabling disclosure' into the following

(i) Disclosure: Anticipatory Art discloses the invention claimed in the patent.

(2) Enablement: An ordinary skilled man would be able to perform the disclosed; invention if attempted to do so by using the disclosed matter: AND common general knowledge.

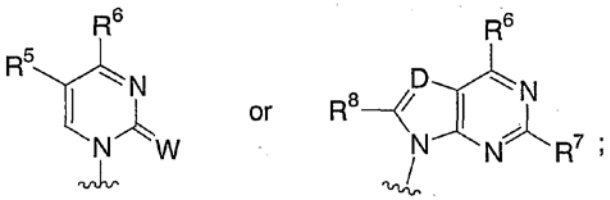
Submissions and arguments of DNP+ and IMAK are as below:

8. Opponents also relied on WO 2002/057425 (WO’425) for lack of Novelty. Opponent argued that the compounds of WO’425 are useful for the treatment of RNA dependent viral infection, in particular as inhibitors of HCV NS5B polymerase, HCV replication and HCV infection. The basic structure of WO'425 is drawn to a sugar attached to a nitrogenous base. They argued that compounds of the impugned patent application '6087 can be arrived by substitution of various substituents of WO'425. In particular, WO’425 discloses formula III.



(III)

Wherein B is

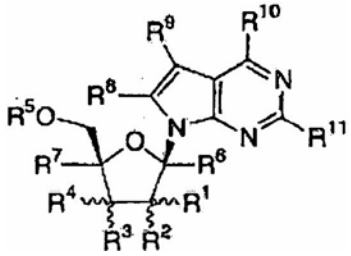


Opponent argues that Claim 5, 6, 7 and 8 of WO'425 provides a match and from these substitutions, the Opponents submit that the Claims 1-16 of the impugned patent application "6087 are anticipated by an individual reading of WO'425.

9. Further, Opponent argued that the synthesis route (glycosylation) prescribed on page 56 (scheme 1) in WO'425 is same as discussed in '6087 on page 74-76. The method of preparation of compounds by glycosylating an appropriately modified sugar involving protecting and deprotecting the functional group involving known regents is disclosed in WO'425.

Submissions and arguments of BDR are as below:

10. Opponent relied on WO 2002/057287 (WO'287) for lack of Novelty. Opponent relied upon following chemical structure of formula I of WO'287



Opponent argues that the Claims 1-16 of the impugned patent application '6087 are anticipated by an individual reading of WO'287.

Further, the synthesis route (glycosylation) prescribed on page 25 (scheme 1) in WO'287 is same as discussed in '6087 on page 74-76. The method of preparation of compounds by glycosylating an appropriately modified sugar involving protecting and deprotecting the functional group involving known reagents is disclosed in WO'425.

Therefore, in light of the disclosure made in the WO'425 application which match all elements of the Claims invention of the impugned patent' '6087 shows that the Claims 1-16 are not novel.

11. I note that Opponent has used both WO'287 and WO'425 interchangeably. However, it is a typo error and during the oral hearings Opponent only referred to WO'287.

Submissions and arguments of Applicant on lack of Novelty are as below:

12. Applicant argued that prior art documents relied upon by the Opponents (WO'425 and WO'287) to argue that the compounds disclosed in them are novelty destroying. Applicant submitted that the cited prior art documents are not novelty destroying in view of the following reasons:-

a.The compounds which the Opponents rely upon are "Hypothetical compounds" and are not specifically mentioned, listed or described in any of the prior art specifications;

b.There is no method for synthesizing the said "Hypothetical compounds", much less any fluorination step;

c. There is no protocol for synthesis or conditions for the manufacture of the "Hypothetical compounds".

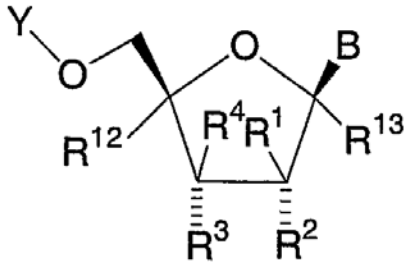
d. There is no disclosure of using DAST to fluorinate any tertiary alcohol at 2'-position of a sugar ring or nucleoside or nucleoside with pyrimidine base.

e. There is no enabling disclosure of the said "hypothetical compounds"; and

f. There is no actual HCV activity which is reported qua the compounds which are sought to be identified by the Opponents.

13. Applicant submitted following chart w.r.t. WO'425 as below:

WO'425

Date of publication	July 25, 2002
Applicant	Merck & CO., INC.
Total compounds synthesized	Over 150 compounds enabled. Opponent highlights particularly examples 46-51, 102 and 103.
Total compounds covered in the Markush	 (I) Multiple Billions of compounds
Activity reported for:	HCV infection
No of compounds reporting activity	Zero – no specific IC50 values. Only a range of less than 100 micromolars on unspecified compounds stated at page 187.
Acknowledged in the Patent specification of Gilead	Yes - At page 12

i. Opponent relies upon a hypothetical structure from this Markush.

ii. This hypothetical compound is not shown or disclosed or enabled in the Specification.

iii. The hypothetical compound is not synthesized in the document;

iv. There is no generalized Scheme even to make the said class of compounds;

v. The hypothetical compound reports no activity;

vi. Hence no motivation to even picks any of these compounds as of the date of filing of the instant application.

14. Applicant submitted following chart w.r.t. WO '287 as below:

WO'287

Date of publication	July 25, 2002
Applicant	Merck & CO., INC.
Total compounds synthesized	38 Examples (27 Base compounds + 3 phosphates)
Total compounds covered in the Markush	(I) Multiple Billions of compounds
Activity reported for:	HCV infection
No of compounds reporting activity	Zero – no specific IC50 values. Only a range of less than 100 micromolars on unspecified compounds stated at page 70
Acknowledged in the Patent specification of Gilead	Yes - At page 12

Opponent relies upon Markush Compound contained at page 5 of the Specification.

i. Opponent draws a hypothetical structure from this Markush.

ii. This hypothetical compound is not shown or disclosed or enabled in the Specification.

iii. This hypothetical compound is with purine base. Gilead's compound has a Pyrimidine base.

iv. Substituents R1 and R2 are attached to C-2 by squiggly lines.

v. R^1 and R^2 can have either the up or down position, but not necessarily

both.

vi. The hypothetical compound is not synthesized in the document;

vii. There is no generalized Scheme even to make the said class of compounds;

viii. The hypothetical compound reports no activity;

ix. Hence no motivation to even picks this compound as of the date of filing of the instant application.

15. Applicant has relied upon following judgments:

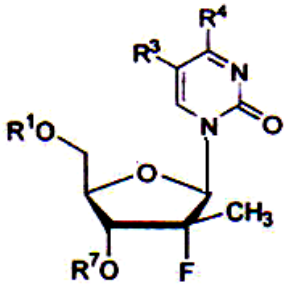
- Dr. Reddy's Laboratories (UK) Ltd. vs. Eli Lilly and Co. Ltd. [2010]RPC 9 --
- Terrell on the Law of Patents (Sweet and Maxwell Publication 2011) – 16thEdn.,-- and
- Patent Law by P. Narayanan (Eastern Law House Publication-2010-4th Edn.).

Essentially, Applicant argued that for a prior art to be novelty destroying, there has to be an enabling disclosure of the compound being relied upon.

ANALYSIS OF NOVELTY:

16. The instant application is directed towards compounds useful for the treatment of *Flaviviridae* infections, including HCV infection. The instant application discloses that HCV infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals. Particularly, instant application discloses (2'R)-2´-deoxy-2'-fluoro (down)-2´-*C*-methyl (up) nucleosides, as well as their corresponding monophosphate, diphosphate and triphosphate forms.

17. Currently pending Claims are directed to a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside of the following formula:



wherein

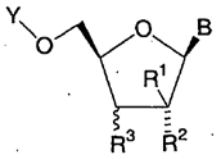
R1 and R7 are independently H, a monophosphate, a diphosphate, or a triphosphate; and

R3 is H and R4 is NH2 or OH.

18. The above formula requires a methyl group (CH3) at the 2' (up) position and a fluorine atom (F) at the 2' (down) position on the sugar ring. I shall refer to nucleosides having this substitution pattern on the sugar ring as "2'-fluoro (down)-2'-methyl (up) nucleosides."

19. The above formula also requires either a cytosine (R4 is NH2) or uracil (R4 is OH) base attached to the sugar ring via the 1-position nitrogen atom (N) in the base ring.

20. Prior art WO'425 – Formula III of WO'425 has following structure.



Formula III

I note that Formula (III) of WO'425, raised by Opponents, is very broad, going on for several pages. The choices of substituents at the 2' position of the furanose ring alone cover about one full page. Formula (III) thus includes billions of compounds, and I do not find any pointer or preference of a substitution pattern of the claimed compounds.

21. WO'425 provides a long list of specific compounds including around 112 compounds on pages 23-24 of the specification. However, none of them anticipate the presently claimed compounds because none of them have the unique 2′-fluoro (down)-2′-C-methyl (up) substitution pattern as claimed by the Applicant.

22. Further, none of compounds provided in Examples 46-51, 102 and 103 relied in opposition statements have a 2′-fluoro (down)-2′-C-methyl (up) substitution pattern, as claimed, and many don't even have the same substituent at the 3' position.

23. Scheme 1 provided on page 56 of WO'425 describes the general synthesis of compounds. There is no fluorination step, at all, in the synthetic route of said Scheme 1 without which fluoro substituent at 2'-position of ribose sugar is not possible. Scheme 1 also does not describe fluorinated starting materials or fluorinating reagents. This is also evident from the fact that none of the compounds mentioned in the examples 1 to 154 on pages 57 to 185 of WO'425 have the unique 2′-fluoro (down)-2′-C-methyl (up) substitution pattern as claimed by the Applicant in instant application.

24. Regarding WO'287, I note that WO'287 discloses compounds all having a purine base, particularly, pyrrolo [2, 3-d]-pyrimidine base.

25. Furthermore, WO'287 has no description of how to make a 2'-fluoro (down)-2'-methyl (up) nucleoside. Scheme 1 is the only general synthetic scheme, and it contains no description of a fluorinated compound or of fluorination at the 2' position of the furanose ring.

26. There is neither exemplification nor enabling disclosure of the claimed compound of the instant application in WO'425. In my view a person skilled in the art will not be able to synthesize claimed compounds in view of the disclosures and from the synthetic route provided in WO'425. The definitions of the various substituents in the prior art documents should be understood in the context of invention contained therein, examples, process for preparation and overall teachings of the document. An arbitrary selection is impossible without hindsight. I agree with the arguments of

Applicant that claimed compounds cannot be deemed to be part of invention as envisaged in WO'425. As noted, WO'287 is not relevant for novelty analysis as it discloses compounds all having a purine base, particularly, pyrrolo [2, 3-d]-pyrimidine base. Accordingly, the claimed compounds are novel and not anticipated in view of cited prior art documents.

SECTION 25(1) (E) LACK OF INVENTIVE STEP AND OBVIOUSNESS:

Arguments submitted by Opponents and Applicant w.r.t. lacks of inventive step are as below:

Submissions and arguments of Optimus, India Care and Sankalp (argued together) on lack of inventive step are as below:

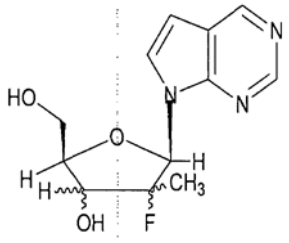
27. During the arguments these Opponents relied upon the following prior art documents for the ground of lack of inventive step:

(a) Prior Patents: WO'2002/057287 (WO'287) or US6348587 (US'587), WO'01/92282 (WO'282), WO'01/90121 (WO'121) and WO'99/043691 (WO'691).

(b) Non-Patent literature: Kevin Park, Panckiewicz et.al. Hayakawa et.al, Wachtmeister et.al, and R. P. Singh et.al.

Submissions on Patent documents:

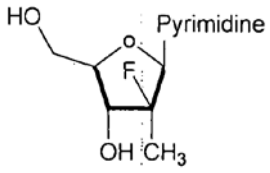
28. While referring WO'287, opponents draw below structure/compound of this prior patent:



The Opponent submitted that WO'287 discloses nucleoside analogues with 2'methyl-up-2'-fluorine-down compounds. The structural representation on the left

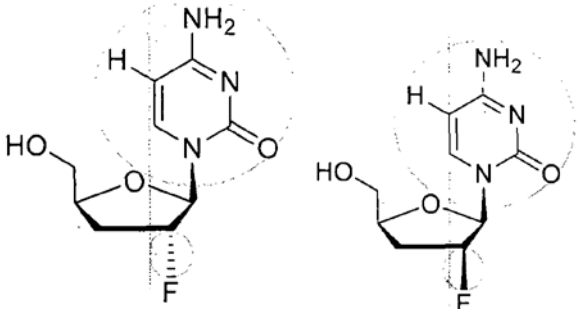
depicts the stereochemistry through Wavy lines which signify that the position of fluorine and methyl is interchangeable at the 2'position. This would imply that the fluorine and methyl groups could be either at the 'up' or 'down position. Opponents submitted that barring disclosing the base of the nucleoside analogue, WO'287 application discloses all components claimed in the impugned invention. The base as disclosed in '287 Application is a purine as opposed to the pyrimidine which is claimed in the impugned invention.

29. From WO'282 and WO'121, opponents draw following structure:



It was argued that the specification of these patent documents make clear reference to compounds of disclosure to be used for the treatment of Flavivirus and pestiviruses. These Patents disclose fluorine in 'up' position and methyl in 'down' position whereas in the impugned specification, fluorine is in the 'down' position and methyl is in the 'up' position.

30. From WO'691or US'587 opponents draw following structure:

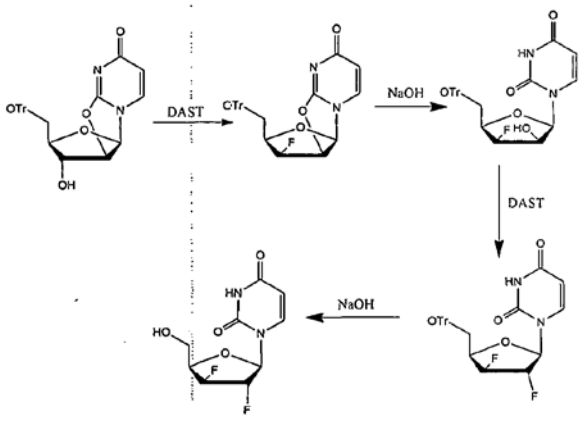


From this document opponent highlighted that this discloses compounds with anti HCV activity and makes references to stereochemically specific fluorines in 'down' position.

Submissions on non-Patent documents:

31. Opponents submitted that teachings in B. Kevin Park, R. Kitteringham motivate a person skilled in the art to carry out modifications at the 2' Carbon position in an attempt to achieve higher anti-HCV activity with low toxicity. Since fluorine is a widely used compound in drug development and due to its importance in altering biological functions without impacting toxicity adversely, a person skilled in the art would be motivated to modify the 2' C position with a fluorine atom.

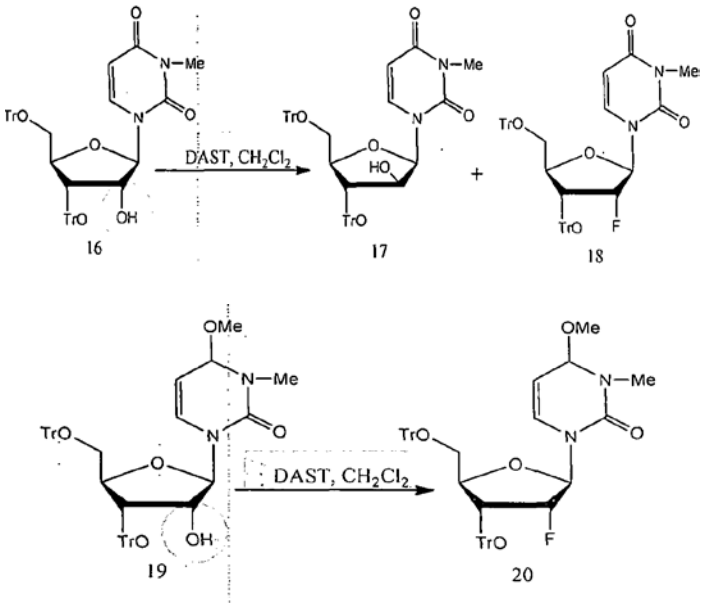
32. Opponents argued that Panckiewicz et al (2000) teaches fluorination of nucleoside using DAST at 2' position on nucleoside analogues were known and used widely. They referred the following scheme in this regard from this document:



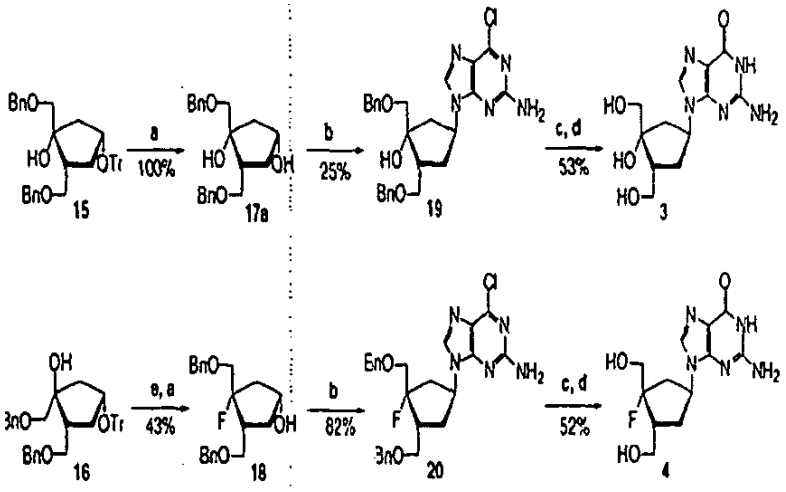
Opponent argued that any person skilled in the art with the aim to introduce fluorine in a desired stereochemical orientation would be able to use the teachings as mentioned Panckiewicz.

33. From the help of Hayakawa et al. it was argued that fluorination of pyrimidine nucleoside using DAST with hydroxyl at 2' position was disclosed. Further, this prior art document also depicts the inversion of configuration. This essentially

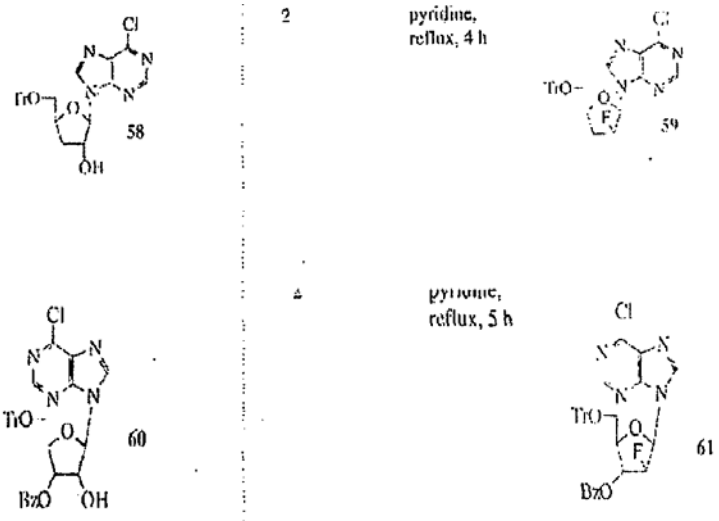
implies that the fluorine is eventually placed in the ‘down’ position and also results in the substitution of the hydroxyl group. They referred the following scheme in this regard from this document:



34. Opponents stated that fluorination using DAST has also been suggested in Wachtmeister. Fluorination of a tertiary alcohol in a cyclopentanol compound with DAST-25% yield, with Deoxo-Fluor-43% yield. This implies that fluorination at the 2’ ‘down’ position can also be carefully controlled even steric hindrance in place. Opponents submitted that Panckiewics and Hayakawa clearly enumerate that the fluorination at the 2’ position can be done through a carefully controlled procedure. Therefore arguments of Applicants that fluorination using DAST results in unpredictable results is not correct. They referred the following scheme in this regard from this document:



35. Opponents argued that R.P. Singh and J.M. Shreeve discloses that fluorination of tertiary alcohols can be successfully achieved by using DAST and deoxoflour as reagents by a person skilled in the art. They referred the following scheme in this regard from this document:



Submissions and arguments of DNP+ and I- MAK on lack of inventive step are as below:

36. These Opponents relied upon the following prior art documents for the ground of lack of inventive step:

a. Prior Patents: WO'2002/057425 (WO'425), WO'01/92282 (WO'282), WO'01/90121 (WO'121) and WO'99/043691 (WO'691) and EP 352248 (EP'248);

b. Non-Patent literature: Middleton et.al, Pankiewicz et.al, Park and Kitteringham et.al 1994, Lino et.al, Wachtmeister et. al. and Steven S Caroll et. al.

Submissions on Patent documents:

37. Opponents referred formula III of WO'425. They argued that the compounds of impugned patent application '6087 may be arrived by substitution of various substituents of WO'425. A person of ordinary skill would able to readily envision (2'R)-2'-deoxy-2'-fluoro-2'-methyluridine as a member of the group in view of the genus. Opponents submitted that the claims of '6087 are obvious in view of WO'425 alone, or in combination with Pankiewicz, which indicates that fluorination of a nucleoside compound is not new and in fact more than 77% of the fluorinated nucleosides synthesized till date contain fluorine at the C-2' of the sugar & includes over 238 compounds. Thus, it is clear that using DAST for fluorination usually results in inversion of configuration but also indicates that for C2' nucleosides this usually gives the configuration with fluorine down.

38. Opponents submitted that Park and Kitteringham, discusses the effect of fluorination on chemical structure, drug action and metabolism and specifically discusses substitution of fluorine into both the base and the sugar residue of nucleosides and nucleotides.

39. Opponents argued that given the disclosures and in view of WO'425, compounds possessing a hydroxyl group below and a methyl group above at the C2' position and the conversion of the hydroxyl group to a fluoro group at the C2' using DAST in the synthesis of Example 94 it is obvious to produce compounds having a fluoro group down and a methyl group above at the C2' position and expect them to have antiviral (HCV) activity.

40. Thus, it would not require an undue amount of experimentation for the person of ordinary skill in the art to arrive at conditions necessary to make (2'R)-2'-deoxy-2'-

fluoro-2'-methyluridine given the disclosure of the '425 application and what was known in the prior art. Fluorination reagents were well known in the art prior to 2000, most specifically diethylamino sulphur trifluoride (DAST) which is the fluorinating agent employed in the '6087 application to make (2'R)-2'-deoxy-2'-fluoro-2'-methyluridine (Middleton). Middleton discloses the use of fluorinating agents such as DAST and dialkylaminosulfur trifluorides to replace hydroxyl group of alcohols with a fluorine group. Further, DAST was well known to react with alcohols to produce alkyl fluoride. The specification need not teach how to make a compound specifically if one of ordinary skill would have known how to do so at the time of filing. Given the use of DAST to convert a C2' hydroxyl to a down C2' fluoro in example 94 of the '425 application it is evident that the '425 application provides a method for converting a C2' hydroxyl to a C2' down fluoro using DAST.

41. Opponent relied upon Formula XI of WO'121. Opponent argued that the compound disclosed in Formula XI is a known form to the claimed compound. Opponents stated that claimed compounds are stereoisomer of the compound disclosed in WO'121. There is only change in the orientation of fluorine downwards in sugar moiety. Opponent further submitted that three of the four halogen analogues are enabled in WO'121 and it would not require one of ordinary skill in the art an undue amount of experimentation to arrive at conditions necessary to make (2'R)-2'-deoxy-2'-fluoro-2'-methyluridine.

42. Opponent relied upon Formula XI of WO'282 The Opponent argues halogens traditionally encompass all four possibilities hence absence of fluoro is not a teaching away to one of ordinary skill in the art. As per the Opponent, WO'282 contains no such explicit teaching away of fluoro at that position. The mere absence of an obvious member of a group in of itself is not an explicit teaching away. The combined teachings of the known members of the halogen class and the WO'282 disclosure would have suggested to those of ordinary skill to try flouro at the 2' position. It is therefore a simple substitution of one known element (chloro, bromo or iodo) for another (fluoro) to give predictable results namely a compound with

antiviral activity. The use of fluoro at the 2'position is therefore obvious to try in view of the '282 application. Furthermore, Pankiewicz (2000) teaches that over 300 fluorinated nucleoside analogus have been prepared and that 77% of these are fluorinated at C2'. Many of these analogs have excellent activity and a person skilled in the art being aware of both WO'282 and Pankiewicz would naturally believe that a combination of these 2 prior art references would render such a substitution pattern obvious.

43. Opponent submits that from WO'691 the modifications with fluorine at 2' position either in the up or the down position of the sugar was already known before the priority date of the impugned patent application '6087. It discloses compounds which have 2'flouro groups in the down position. This is also admitted by the applicant.

44. The Opponent argues that EP'248 discloses compounds and methods to make the compounds which have 2'flouro group in the down position. Further the concept of using fluorine at 2' position is already known in the prior art. EP'248 also teaches that DAST result in inversion of configuration.

Submissions on non-Patent documents:

45. Opponents argue that Steven S Caroll provides information that 2' modifications of natural substrate nucleosides transform these molecules into potent inhibitors of HCV replication. It establishes the activity of 2'C-methyladenosine and 2'O-methylcytidine as inhibitors of NS5B-catalysed RNA polymerase in HIV infected cells.

46. Opponents argues that Lino et. al. shows the usefulness of uridine derivtives as early as 1996, which along with other prior arts discussed would have motivated and made it obvious to try for methyluridine as claimed in '6087.

47. Opponents argue that Middleton discloses the use of DAST to prepare fluorides from tertiary alcohol. DAST was well known to react with alcohols to produce alkyl

fluorides in the prior art. Method of fluorination was already known to the person skilled in the art.

48. Opponent argues that Pankiewicz, teaches that fluorine and hydroxyl groups are isostere and are easily interchangeable was known in the prior art. Thus, the concept of using DAST for the conversion of hydroxyl group to fluorine was known as long known before the priority date of the impugned patent application '6087. A person skilled in the art being aware of both WO'282 and Panckiewicz would naturally believe that a combination of these two prior art references would render such a substitution pattern obvious.

49. Opponents argues that Park BK and Kitteringham NR shows the usefulness of fluorine substitution which along with other prior art discussed here, would have motivated and made it obvious to try the use of fluorine at the 2' position of the nucleoside analogues. It discloses that fluorine has been substituted into both the base and the sugar residue of nucleosides and nucleotides and the resulting compounds represent an important group of drugs. Further, the concept of the method of fluorination of the nucleoside analogues was also known to a person skilled in the art. For a person skilled in the art, the isosteric substitution of hydroxyl group with fluorinate nucleoside analogues would be obvious.

50. Opponents argue that from Wachtmeister Tetrahedron it was well known and recognized in the nucleoside field that DAST reacts readily with tertiary alcohols. Thus a skilled person in the art would have chosen DAST as fluorinating agent for converting OH into F.

51. As per the Opponent, mosaicing of all above elements of cited prior art documents such as Middleton et.al, Pankiewicz et.al, Park and Kitteringham et.al, Lino et.al, WO'691 and EP"248, would lead to the conclusion that instant application is obvious.

52. Opponent also relied on KSR International Co. vs Teleflex Inc. 550 U.S. 398 (2007) for the lack of inventive step argument.

Submissions and arguments of BDR on lack of inventive step are as below:

53. These Opponents relied upon the following non documents for the ground of lack of inventive step: Matsuda et.al, Hertel et.al, Middleton et.al, and Maybridge Medchem et.al

Submissions on non-Patent documents:

54. Opponent argue that from Matsuda et al, the presence of the methyl group at the 2' position in the up configuration is already known and well established prior to the priority date of the '6087.Compounds disclosed in Matsuda contain a sugar molecule substituted with a nitrogenous base at 1' position, methyl group at 2' position in the up configuration & a hydroxyl group in the down position and a hydroxyl group at 3' position. POSA would readily know and also would apply prior art both generally known in medicinal chemistry basic teachings (-F as a bioisostere for OH) as well as the knowledge that –F is useful in analogs of nucleosides for enhancing and prolonging biological activity. It would not require an undue amount of experimentation for a person of ordinary skill in the art to arrive at conditions necessary to make (2'R)-2'-deoxy-2'-fluoro-2'-methyluridine given the disclosure of the Matsuda et al and what was known in the prior art.

55. Opponents argue that all the compounds disclosed by Hertel et al have a di-fluoro substitution at the 2' position both in the up configuration and in the down configuration. It can be clearly seen that the presence of fluoro group in the down configuration at 2' position of the sugar molecule of nucleoside analogues is already known. The compounds disclosed also possess anti-viral activity. Thus, fluorination of the nucleoside compounds is not a new concept.

56. Opponents relied upon Middleton to argue that it discloses the use of DAST to prepare fluorides from tertiary alcohol. DAST was well known to react with alcohols to produce alkyl fluorides. Fluorination reagents were well known in the art prior to 2000 most specifically diethylamino sulfur trifluoride (DAST) which is the

fluorinating agent employed in the '6087 application to make (2'R)-2'-deoxy-2'-fluoro-2'-methyluridine.

57. Opponents also relied on Maybridge Medchem to argue that it provides information that hydroxyl and fluorine are isosters. For a person skilled in the art, the isosteric substitution of hydroxyl with fluorinate analogues would be obvious.

58. As per the Opponent, mosaicking of all the elements of cited prior art such as Matsuda et.al, Middleton et.al, Hertel et.al, Maybridge Medchem et.al, would lead to the conclusion that instant application is obvious.

Submissions and arguments of Applicant on lack of inventive step are as below:

59. Applicant argued that specification of the patent application is quite elaborate and has dealt with all most all the relevant documents cited by the opponents. Applicant argued that the patent related documents which have been relied upon by the Opponents and duly acknowledged in the specification are;

i. WO 2002/057425 (WO'425) - line 1, page 12 of original PCT application.

ii. WO2001/92282 (WO'282) - lines 8-16 pages 8 and lines 11-15, page 11 of original PCT application.

iii. WO2001/90121 (WO'121) - lines 11-15, page 11 of original PCT application.

iv. WO2002/057287 (WO '287) - lines 9-11, page 12 of original PCT application.

v. WO 1999/43691 (WO '691) and US 6348587 (US'587) - lines 15- 20, page 12 of original PCT application.

60. Applicant submitted that arguments of the Opponents on the ground of lack of Inventive Step are two fold;

a. That the class of nucleosides was known for antiviral activity and all that required was fluorination at the 2' position of the nucleosides.

b. Alternatively it was argued by the Opponents that the exact compound with methyl up and hydroxyl down configuration at 2' position of nucleoside were known and that fluorine is a mimic of hydroxyl OR that Flourine is a bioisostere of OH, and hence the compounds of the present invention are obvious.

61. Applicant submitted that for obviousness analysis the prior art documents cannot be viewed at with hindsight. Applicant submitted that from prior art documents on record it is evident that there were a large number of researchers who were working in this field attempting to find an effective and safe treatment for HCV infection. The documents of the prior art, including the patent documents the Opponents cited for alleged invalidity, reveal that some other researchers were focused on nucleosides with methyl up and hydroxyl down at 2' position. However, there was no motivation or suggestion that a combination of methyl up and fluorine down at the 2' position of the nucleoside with pyrimidine base could create an effective compound for treatment of hepatitis C. In fact, some of the documents in the prior art either considered fluorine singly at the 2' position or only considered use of other halogens such as chlorine, bromine, iodine at the 2' down position and not fluorine (WO '282& WO '121). As late as of end April, 2003 researchers in this field of research reported that a mono-substituted fluorine at the 2' position showed compounds which were inactive or less active. Thus, the common general knowledge available on the date of priority reveal that there was not a single document which considered or even remotely suggested fluorine at the 2' down position and methyl at the 2' up position to result in a compound which would act as complete treatment for hepatitis C.

62. Applicant argues that analysis of all prior art documents shows that fluorination using DAST was very unpredictable and relied upon following references:

a. Elimination (dehydration) resulting in a mixture of products - Middleton;

b. Rearrangement of the molecules – Middleton;

c. Inversion of configuration in the resultant fluorinated product – Pankiewicz;

d. Creation of a mixture of two compounds instead of one - Hayakawa et al., Wachtmeister et al, and Middleton;

e. Retention of configuration in the resultant fluorinated product - Pankiewicz et al and Hayakawa et al; and

f. No fluorination occurring - Pankiewicz et al, Hayakawa et al.

It was submitted that treatment of an alcohol with DAST was not known to automatically result in fluorination with inversion of configuration or in the retention of the configuration. Stereochemistry of compounds after fluorination using DAST is substrate-specific. Accordingly, it would have required a great deal of experimentation in order for one skilled in the art to arrive at a method of making nucleoside with the following unique combination of;

i. A nucleoside (sugar + base);

ii. With the pyrimidine base;

iii. Substitution at the 2’ position;

iv. Bi-substitution at the 2’ position;

v. Methyl at the 2’ up position; and

vi. Fluorine at the 2’ down position.

Applicant submitted that nucleoside with the above structural features related to a breakthrough invention which is a full treatment for HCV infection was neither known nor contemplated in any of the documents cited by the Opponents.

63. Applicant has filed separate sheet of arguments for main prior art documents along with written submission in support their argument on inventive step. Their basic arguments on the main patent documents viz. WO'425, WO'287, WO'121 and WO'282 are as under:

a) Opponents have drawn a hypothetical structure/compound from the Markush of these patent documents. In other words Opponents have not started their analysis of inventive step with exemplified compound or structure.

b) In all these patent documents there were number of substituents provided for substitution at multiple position of the markush formula. Applicant argued that with the all possible permutations it would billions of possibilities for arriving at the structure of the hypothetical compound. Applicant further argued that in view of teachings of these patent documents it is difficult to arrive at these hypothetical compounds without hindsight.

c) Applicant also urged that the method or process for preparing the compounds provided in these patent documents would not lead to these hypothetical compounds.

d) Opponents have given no reason as to what is the motivation to pick the hypothetical compound out of the billions possibilities and also that there is no example having Methyl UP combined with Flourine DOWN at 2'position;

e) Applicant argued that modification of the prior art compounds such as 2'Me/OH is not possible without Hindsight. Several fluorinating agents were available in the prior art. There was no reason to use DAST only. DAST chemistry is

highly unpredictable i.e., it could result in Elimination or Rearrangement. Also, DAST chemistry is highly dependent not only on the substrate, but on the exact reaction conditions, solvent, protecting group strategy, and other factors, none of which is described. Opponents have not discharged their burden.

f) Applicant argued that opponents have not shown any documents showing Fluorination on Tertiary alcohol at 2'position of Sugar or Nucleoside using DAST. Applicant argued that as on the priority date there was no description how to install Fluorine on Tertiary alcohol at 2'position of Sugar or Nucleoside using DAST.

g) Applicant argued that even in hindsight, using DAST with the enabled compounds of some prior art documents especially WO'287 would not lead to claimed compounds of present invention i.e., Pyrimidine based nucleosides having CH3(UP) and F (DOWN) at 2' position.

h) IN respect of WO'121 and WO'282 it was argued that all compounds under the Markush (XI) have either hydrogen (H), bromine (Br), or a nitro group (NO2) as the 2' (down) R7 substituent. Applicant argued that Formulae (XI), (XVI), (XVII) and (XVIII), chlorine, bromine and iodine are the only halogens permitted at the 2' (down) R7 position, suggesting that fluorine was omitted purposefully, which is a negative teaching or a "teaching away."

64. Park et al.

i. Park et al. is areview article discussing the effect of fluorine substitution on drug metabolism in general. It does not mention any nucleoside-based drug for HCV treatment.

ii. With respect to Park et al. Opponent has not applied any of the purported effects to the context of this invention.

iii. Opponent has not shown specifically how Park et al. render any one particular aspect of the present invention obvious.

iv. By raising an extremely broad set of general concepts, from ligand binding to distribution and metabolism, the Opponent seems to be suggesting any and all possible concepts which *might* apply to the present invention, but have not been able to show how any specific concepts actually could or do apply.

v. Opponent's argument relies on gross assumptions that the Opponent makes across the entire field of medicinal chemistry without showing that it is appropriate to do so, and without applying these assumptions to the particular subject matter of invention, i.e. nucleotide analog inhibitors of HCV RNA polymerase. Opponent's arguments should be rejected on this basis alone.

vi. Opponent relies on Compound 32, which has a purine base instead of a pyrimidine (e.g., cytosine or uracil) base, F is at 2' (up) position, 2' is monosubstituted, and no substitution at 3' position.

vii. On page 623 last para it states that "the success of 5-fluorouracil as an antimetabolite has prompted the continued search for fluorinated purine and pyrimidine compounds as potential anticancer agents and more recently as drugs for use in treatment of HIV disease."

65. Gumina et al.

i. Gumina et al. describes synthesis of L-2',3'-dideoxy-3',3'-difluoro- and **L**-2',3'-didehydro-2',3'-dideoxy-3'-fluoro nucleosides.

ii. The key fluorination step involved is for conversion of ketone to difluoro intermediate using DAST, not for an alcohol let alone for a tertiary alcohol.

iii. Opponent has not applied any of the purported effects to the context of this invention.

iv. Opponent has not shown specifically how Gumina et al. renders any one particular aspect of the present invention obvious.

66. Pankiewicz

i. Pankiewicz “a review article” discusses various fluorinated nucleosides, including nucleosides with fluorine at the 2’ (including doubly fluorinated at 2’), 3’, 4’, and 5’ positions.

ii. It does not suggest compounds with 2’-fluoro (down)-2’-methyl (up) substitution pattern.

iii. It does not teach how to make the compound with 2’-fluoro (down)–2’-*C*-methyl (up) substitution pattern.

iv. Indicates that the inherent characteristics of the 2’ carbon in nucleosides make it difficult to add fluorine to that position in a stereospecific manner.

v. It notes that as the 2’ carbon is intrinsically less reactive than other carbons in the sugar moiety and because fluorine is a weak nucleophile, “direct nucleophilic displacement of a good leaving group in the 2’-*ribo* configuration with fluorine has been considered to be difficult, if not impossible …” .

vi. Pankiewicz focuses on fluorination of primary and secondary carbons, not tertiary carbons.

vii. However, DAST is highly unpredictable.

viii. Fluorination is VERY difficult and unpredictable.

ix. The ref states on internal page 94 right column, that “direct nucleophilic displacement of a good leaving group in the 2’-ribo configuration with fluorine has been considered to be difficult, if not impossible, not only due to poor activity of C-2’, but also due to weak nucleophilicity of fluorine, which in addition is known as a rather strong base”.

67. Middleton

i. It teaches the fluorination of certain sensitive alcohols and aldehydes.

ii. Middleton does not specify any nucleosidic compound.

iii. It does not discuss the use of DAST to fluorinate any carbohydrate ring or sugar ring let alone be the sugar ring of a nucleoside.

iv. Middleton does not discuss the use of DAST to fluorinate a tertiary alcohol on sugar ring of a nucleoside.

v. In fact, Middleton discusses certain limitations of using DAST when fluorinating isobutyl alcohol and borneol, noting that a mixtures of products resulted.

vi. Middleton also discloses that the reaction between DAST and even a secondary alcohol in a cyclic substrate, cyclooctanol, can result in elimination (30% cyclooctene obtained along with cyclooctyl fluoride).

vii. Even if DAST had been shown to successfully fluorinate, e.g., certain straight chain alcohols, one skilled in the art could not have predicted that DAST would work to fluorinate a sterically hindered tertiary alcohol at the 2' position of a nucleoside's sugar ring.

viii. Complete hindsight gained from Applicant's present application----the first publication teaching the synthesis of a (2'R)-2'-deoxy-2'-fluoro (down)-2'-*C*-methyl (up) nucleoside using DAST.

ix. Opponent relying on page 576, where DAST is used to fluorinate seconadry alcohol

68. Wachtmeister et al.

i. Discusses the synthesis of 4-substituted carbocyclic 2,3-dideoxy-3-C-hydroxymethyl nucleoside analogues (3) and (4) by fluorinating Intermediate 16 with Deoxofluor.

ii. Treatment with DAST resulted in a mixture of products.

iii. Intermediate 16 is a carbocyclic compound with an alcohol at the 4-position, whereas the Gilead's invention have pentose sugars with alcohols at the 2'-position.

iv. Carbocyclic sugar analogs (or carbocyclic nucleoside analogs) differ electronically from pentose sugars (or nucleosides containing pentose sugars).

v. The difference is significant as the degree of steric hindrance varies for the different positions on the sugar ring of a pre-formed nucleoside.

vi. Electronic effects also differs between the 2' position and other positions on the sugar ring, eg., due to the 2' carbon's proximity to the anomeric center.

69. Maybridge Medchem

i. Drugs and other biologically active chemicals discussed are different in terms of both chemical structure and biological function.

ii. Maybridge MedChem does not discuss nucleosides or nucleotides, or antiviral compounds at all.

iii. Maybridge MedChem at 2-3 ("Despite the fact that fluorine has a greater size than hydrogen, several studies have demonstrated it as a reasonable hydrogen mimic. The replacement of hydrogen by fluorine is thus an extensively used technique in medicinal chemistry …."). The present application also states that "fluorine is known to be capable of forming a hydrogen bond but unlike a hydroxyl group, which can act both as a proton receptor and proton donor, fluorine acts only as a proton acceptor" (page 45 of original PCT application).

iv. The 2' (down) fluorine atom does not engage in the same type of bonding with the NS5B enzyme that a 2' (down) hydroxyl group does; rather, the fluorine atom appears to disrupt such interactions.

v. Maybridge Medchem does not mention anything regarding anti- HCV studies / experimental data.

vi. Maybridge MedChem would not have suggested to an artisan to replace a 2' (down) hydroxyl group (e.g., in a 2'-hydroxy (down)-2'-methyl (up) nucleoside) with a fluorine atom so as to arrive at the claimed compounds.

vii. It mentions trifluoromethyl group enhances metabolic stability.

70. Hayakawa et al.

i. It discusses reaction of DAST specifically with nucleosides having 2',3'-vicinal diol systems.

ii. It does not discuss the use of DAST to install a fluorine atom on a tertiary alcohol at a nucleoside's 2' position.

iii. The final products differ structurally from the presently claimed compounds, and lack the 2'-fluoro (down)-2'-*C*-methyl (up) substitution.

iv. Hayakawa et al. does not describe any DAST reaction that provides a tertiary fluoride, let alone at a nucleoside's constrained and sterically hindered 2' position.

v. Even further, Hayakawa et al. demonstrates the unpredictability of DAST fluorination reactions. See chart 1 conversion of 5 to mixture of 6 and 7 with DAST, suggests that 7 is formed from 5 with inversion of configuration, competing with the intramolecular cyclization.

vi. In fact, with one of the substrates, only intramolecular cyclization occurs producing unfluorinated 2'-cyclo derivative showing failure to give a fluorinated product. At page 1137 conversion of compound 14 to 15.

vii. On the other hand, in chart 3 at page 1137, a mixture of products (17 & 18) is obtained using DAST with compound 16.

viii. In chart 4 at page 1137, fluorination proceeds with retention of configuration using DAST, conversion of compound 19 to 20.

ix. It states that "the unexpected retention of configuration during the formation of 18 and 20 would be explicable in terms of neighboring group participation by the respective O2-atom which compels the fluoride anion to attack from the α-side.

x. DAST chemistry is unpredictable - See chart 3 and 4 on page 1137.

71. Matsuda et al.

i. It does not disclose or suggest compounds with 2'-deoxy-2'-fluoro (down)-2'-methyl (up) substitution pattern.

ii. Contain no reference to fluorinated nucleosides or processes of fluorination for making such compounds.

iii. As per Matsuda's teaching 2'-deoxy-2'-methyl compound 7 was the most active against the mouse leukemic cell line tested (page 3969-70). The skilled artisan would also understand that an anti-leukemic (or anti-cancer) agent would be acting as DNA and that natural DNA nucleosides have a hydrogen in the 2' (down) position. The skilled artisan would understand that a nucleoside with anti-HCV (or

anti-*Flaviviridae*) activity would be acting on RNA and that natural RNA nucleosides have a hydroxyl in the 2' (down) position.

iv. Anti-cancer agents typically work by killing the cell, whereas anti-HCV agents must be anti-viral but retain cell viability.

v. Thus, the Opponent's bioisostere argument about replacing a 2' (down) hydroxyl group in a Matsuda et al. compound with a fluorine atom clearly relies on impermissible hindsight, as it is premised on selecting and modifying a compound that the reference teaches is not the most active in order to arrive at a compound with a type of biological activity that the reference does not discuss.

72. Herdewijn et al.

i. Herdewijn et al. refers to three methods to synthesize nucleosides fluorinated in the sugar moiety:

- Epoxide cleavage by fluoride ions,
- Displacement of a sulfonyloxy group by fluoride ions, and
- Opening of the anhydro bond formed by the sugar and the base part.

ii. Herdewijn et al. nowhere discusses the use of DAST to install a fluorine atom on a tertiary carbon at a nucleoside's 2' position.

iii. First method of Herdewijn et al. is ring opening of an epoxide on a sugar moiety with a fluoride ion using fluorinating reagents Et_4NF/acetonitrile and KHF2/ethylene glycol, not DAST.

iv. It reports use of 10% HF in dioxane for fluorination via epoxide ring opening.

v. Herdewijn et al discusses the second method, i.e., nucleophilic displacement of sulfonates by fluoride ions, for the introduction of a fluorine atom in the 5'-position of a nucleoside with respect to primary and secondary carbons using reagents such as potassium fluoride, tetrabutylammonium fluoride, HF, and TASF.

vi. The third method discussed by Herdewijn et al. involves nucleophilic attack on anhydro bonds using HF (with catalytic AlF3 in some cases), potassium fluoride, KHF_2, or NH_4F.

vii. Herdewijn et al. discusses the use of DAST.

viii. No examples of displacing a tertiary hydroxyl with a fluorine on a sugar or carbohydrate are given.

ix. Herdewijn et al. does not teach the use of DAST to fluorinate a tertiary carbon at the 2' position of a nucleoside.

73. Harada et al.

i. Harada et al. discusses a variety of compounds stated to have inhibitory activity against cancer, herpes simplex viruses type 1 and 2, Varicella zoster virus, and cytomegalovirus.

ii. Harada et al. is directed towards 5'-deoxyanalogues of FIAC (2'-fluoro-5-iodo-arabinosyl cytidine), FIAC (2'-fluoro-5-iodo-arabinosyl uridine) and FMAU (2'-fluoro-5-methyl-arabinosyl uridine).

iii. Different in terms of both chemical structure and biological activity.

iv. Harada et al. does not even discuss bioisosteric replacement of a hydroxyl group with fluorine. Rather, Harada et al. explores replacing the 5'-hydroxy group in FIAC and FMAI with hydrogen or SH, which was found to reduce or eliminate antiviral activity.

v. Anti-cancer agents typically work by killing the cell, whereas anti-HCV agents must be anti-viral but retain cell viability.

vi. The 2' (down) fluorine atom does not engage in the same type of bonding with the NS5B enzyme that a 2' (down) hydroxyl group does; rather, the fluorine atom appears to disrupt such interactions.

74. De Francesco and Rice

i. Review articles discussing various potential approaches for treating HCV infection.

ii. Opponent relies on compound 13 i.e. □-D-2'-methyl-ribofuranosyl-guanosine.

iii. Compound 13 lacks both 2'-deoxy-2'-fluoro (down)-2'-methyl (up) substitution and a cytosine or uracil base,

iv. Given the structural differences between β-D-2'-methyl-ribofuranosyl-guanosine and the presently claimed compounds, one skilled in the art would not have been able to predict the high anti-HCV activity and low toxicity of the compounds of the instant invention.

v. Complete hindsight gained from Applicant's present application.

75. De Francesco et al.

i. Review articles discussing various potential approaches for treating HCV infection.

ii. Opponent relies on compound 11 i.e. β-D-2'-methyl-ribofuranosyl-guanosine

iii. Compound 11 lacks both 2'-deoxy-2'-fluoro (down)-2'-methyl (up) substitution and a cytosine or uracil base,

iv. Given the structural differences between β-D-2'-methyl-ribofuranosyl-guanosine and the presently claimed compounds, one skilled in the art would not have been able to predict the high anti-HCV activity and low toxicity of the compounds of the instant invention.

v. It states that the therapeutic approaches for HCV infection known till 2003 are not very efficacious and plagued with many unwanted side effects.

76. Walker and Hong

i. Review articles discussing various potential approaches for treating HCV infection.

ii. Opponent relies on compound (c), i.e. β-D-2'-methyl-ribofuranosyl-guanosine.

iii. Compound (c) lacks both 2'-deoxy-2'-fluoro (down)-2'-methyl (up) substitution and a cytosine or uracil base,

iv. Given the structural differences between β-D-2'-methyl-ribofuranosyl-guanosine and the presently claimed compounds, one skilled in the art would not have been able to predict the high anti-HCV activity and low toxicity of the compounds of the instant invention.

v. Opponent highlights Page 6, column 1, placitum 1-6. There only it states that "however detailed biological information is yet not available, making it difficult to evaluate the mechanism of action of these nucleosides".

vi. Complete hindsight gained from Applicant's present application.

77. Walker et al.

i. Review articles discussing various potential approaches for treating HCV infection.

ii. In fact, the Abstract states that "this review summarizes current and evolving treatments for chronic hepatitis C infection. In addition, progress in HCV targets and drug discovery tools valuable in search for anti-HCV agents is detailed".

iii. Opponent relies on compound (a) & (c), i.e. 2'-methyl adenosine & 2'-O-methyl-cytidine.

iv. Both the Compounds (a) & (c) lacks 2'-deoxy-2'-fluoro (down)-2'-methyl (up) substitution.

v. Given the structural differences between 2'-methyl-adenosine or 2'-O-methyl-cytidine and the presently claimed compounds, one skilled in the art would not have been able to predict the high anti-HCV activity and low toxicity of the compounds of the instant invention.

vi. Complete hindsight gained from Applicant's present application.

78. Carroll et al.

i. It provides compounds with 2'-methyl (up) – 2'-hydroxy (down) substitution pattern for purine bases and only mono substituted compound for pyrimidine bases.

ii. Carroll et al. teaches that nucleoside compound with purine bases i.e. 2'-C-methyl-adenosine is significantly more active than nucleoside compound with pyrimidine base i.e. 2'-O-methylcytidine, a negative teaching to person skilled in the art.

iii. Carroll et al., does not describe how to make a 2'-deoxyribonucleoside compound with a 2'-fluoro (down) – 2'-methyl (up) substitution pattern at 2'-carbon of ribose sugar moiety.

iv. It states that whether the compounds, 2'-C-methyl-adenosine and 2'-O-methylcytidine, have pharmacokinetic and safety profiles sufficient for their developments as HCV therapeutics, is uncertain and questionable.

79. Eldrup et al., Bhat et al. & Olsen et al.

i. These references are cited in the present application's specification on page 13.

ii. Contrary to Opponent's assertion, neither Eldrup et al., nor Bhat et al., give a detailed account of the "structure-activity relationship at the 2' position."

iii. Instead, they give limited accounts of nucleoside analogs that mostly have a single non-hydrogen substituent at the 2' position.

iv. The only 2' di-substituted compounds have either –OH/-methyl or –O-methyl/-methyl at the 2' position.

v. These references to not discuss 2'-di-substituted compounds having a fluorine at the 2' (down) position.

vi. In fact, if anything, Eldrup et al., teaches away from the present invention as it describes that compounds with a 2'-fluoro (down)substituent and hydrogen at the 2' (up) position showed much worse anti-HCV activity than the corresponding 2'-hydroxy (down)-2'-methyl (up) compounds.

80. Standring et al.

i. Opponent has provided only the abstract of Standring et al.'s presentation, which does not provide structural information regarding NM107 or NM283 other than to describe NM107 as a "ribonucleoside analog" and NM283 as "a prodrug form of NM107."

ii. It does not even disclose the structures of NM107 or NM283, let alone disclose or suggest the structures of the (2'R)-2'-deoxy-2'-fluoro (down)-2'-*C*-methyl (up) nucleosides. It does not teach or suggest how to make the presently claimed compounds.

iii. Even if one were to consider the Opponent's comment in paragraph 72 regarding NM107's *later*-disclosed structure, such structure would not render the instant claims obvious.

iv. At a minimum, NM107 lacks the 2'-deoxy-2'-fluoro (down)-2'-*C*-methyl (up) substitution required by the instant claims.

81. Park et al.

i. Very general document on the metabolism of fluorine-containing drugs.

ii. Park et al. discusses a variety of drugs and other biologically active chemicals that are very different from the compounds of the present application in terms of both chemical structure and biological function.

iii. The 2' (down) fluorine atom does not engage in the same type of bonding with the NS5B enzyme that a 2' (down) hydroxyl group does; rather, the fluorine atom appears to disrupt such interactions.

82. R. P. Singh et al.

i. Singh et al. discusses introducing fluorine into certain organic compounds using Deoxofluor and DAST.

ii. Singh et al. does not teach or suggest using Deoxofluor or DAST on tertiary alcohols at a nucleoside's 2' position.

iii. However, Singh et al. does illustrate the unpredictability of fluorination chemistry as of the present application's filing date.

iv. For example, Singh et al. illustrates that attempted fluorination reactions could result in elimination (rather than fluorination) and rearrangement products.

v. This unpredictability is one reason that an artisan could not have made the claimed compounds without extensive experimentation.

83. WO'691 (US'587)

i. Compounds of WO'691 do not have a 2'-fluoro (down)–2'-*C*-methyl (up) substitution pattern.

ii. Compounds of WO'691 are only mono-substituted at the 2' position of sugar moiety.

iii. WO'691 further provides no guidance concerning the synthesis of nucleosides having a (2'R)-2'-fluoro (down) – 2'-*C*-methyl (up) substitution pattern.

iv. WO'691 does not contain any data for anti-Hepatitis C activity assay.

84. Lino et al.

i. Lino et al. discloses a synthetic method for (2'S)-2'-*C*-alkyl-2'-deoxyuridines.

ii. Iino et al.'s compounds do not have or suggest a 2'-fluoro (down)–2'-*C*-methyl (up) substitution pattern.

iii. It is silent and does not provide any hint about the use of a halogen, much less a fluorine atom, at the 2' (down) position.

iv. Iino et al. is directed to the synthesis of nucleosides having only one non-hydrogen (alkyl) substituent at the 2'-position.

v. It does not describe how to make a compound with a 2'-fluoro (down)–2'-methyl (up) substitution pattern.

vi. Iino et al. comments that certain nucleosides with (2'S)-2'-deoxy-2'-C-methyl or (2'S)-2'-deoxy-2'-C-fluoromethyl substitution have shown antitumor or anti-HSV activity.

85. EP352248 (WO'036)

i. WO'036 relates to L-ribofuranosylnucleoside analogues.

ii. WO'036's compounds have only a single non-hydrogen substituent, R^1, at the 2' position.

iii. Compounds of WO'036 have an L-configuration at C-4 of the sugar ring, whereas the presently claimed compounds have a D-configuration at the C-4 position.

iv. It states on page 6 of the ref that "the compounds of formula (I) inhibit the activity of reverse transcriptase of retroviruses including HIV.

v. WO'036's Markush formula does not even encompass, let alone disclose, the presently claimed compounds.

86. Hertel et al.

i. It describes the synthesis of certain 2-deoxy-2,2-difluoro-D-ribofuranosyl nucleosides.

ii. As Hertel et al.'s Compounds 8 and 12 are di-fluorinated at the 2' position, their synthesis does not require the same type of stereochemical considerations involved in making the claimed compounds.

iii. It does not teach how to install both a methyl group and a fluorine atom at the 2' position, let alone how to do so with the specific stereochemistry required by the present application's claims.

iv. It does not specify the activity of the compounds disclosed therein. In fact, Hertel et al. discusses research done pursuant to a program "initiated with hopes of finding compounds of potential value as anticancer and/or antiviral agents" (abstract) and "with hopes of finding some unique biological activity" (page 2406).

v. Hertel et al. contains no suggestion that replacing a hydroxyl group (i.e., OH) in a Matsuda et al. compound with a fluorine atom would give a nucleoside with anti-*Flaviviridae* activity, let alone with anti-HCV activity.

vi. Complete hindsight gained from Applicant's present application.

87. Applicant has also argued that the corresponding patent application has been granted in many countires. Further, in the reply statement and during hearing, Applciant relied upon a few decision from the foreign jurisdiction in favour of this application for novelty and inventive step. Applicant aruged that medicine manufactured from the claimed compounds of the patent application is an approved drug worldwide including India.

Case laws relied upon by the parties:

88. Opponent refers to following case laws for test of inventive step:

i. Four steps test mentioned in the Windsurfing International vs Tabur Marine (Great Britain) 1985 WL 310551;

ii. Biswanath Prasad Radhe Shyam v. Hindusatan Metal Industries (1979) 2SCC 511;

iii. Glaverbell SA vs. Dave Rose and ORS;

iv. KSR International Co. vs Teleflex Inc 550 US 398;

v. In Re O'Farrell- 853 F.2d 894 (Fed. Cir. 1988); and

vi. ln re Francis S. Gurley 27 F. 3d 551 (1994)

89. Applicant relied upon following case laws for test of inventive step:

i. F. Hoffmann La Roche Ltd. and Anr. V. Cipla RFA(OS) 92/2012 and RFA (OS) 103/2012;

ii. Terrell on the Law of Patents (Sweet and Maxwell Publication 2011) – 16thEdn.

iii. Raj Prakash v. Mangat Ram Chowdhary and Ors. AIR 1978 Delhi 1;

iv. Ajay Industrial Corporation Delhi v MrShirokanao of Ibaraki City, Osaka, Japan 1983 PTC 245;

v. Vickers, Sons & Co. v Siddell 1890 RPC 292;

vi. Pope Alliance v Spanish River Pulp and Paper Mills Ltd; A.I.R. 1929 Privy Council 38; and

vii. Terrell on the Law of Patents (Sweet and Maxwell Publication 2011) – 16th Edn.

viii. Technograph Printed Circuits Limited v. Mills & Rockley (Electronics) Limited; 1972 RPC 346;

ix. Non-Drip Measure Coy. Ltd. v. Stranger's Ltd. and Ors. – [1943] 60 RPC 135; and

x. Terrell on the Law of Patents (Sweet and Maxwell Publication 2011) – 16th Edn.

ANALYSIS OF INVENTIVE STEP:

90. I have gone through all the prior art documents, opposition petitions, replies and written note of arguments by the parties. During the arguments, Applicant's main points were that there is no prior art documents showing fluorination at 2' position on a tertiary alcohol of a nucleoside or sugar of nucleoside, various methods of fluorination prescribed in the prior art documents, unpredictability of DAST, hypothetical compounds from prior patent not possible in the hindsight and lack of guidance of synthetic route to arrive at claimed modification at the 2' position of sugar moiety of the nucleoside.

91. Opponent relied upon Formula (III) of WO'425. The specification provides number of possible substitution at various positions. A person skilled will have to consider a large number of possible substituents at the 2' position of the furanose ring. I agree that Formula (III) if not billions of compounds at least millions. WO'425 provides list of specific 112 compounds. Compounds enabled in this patent do not have a 2′-fluoro (down)-2′-*C*-methyl (up) substitution pattern, as claimed, and many don't even have the same substituent at the 3' position. From the teachings of WO'425 it would be difficult for a person skilled to arrive unique 2′-fluoro (down)-2′-*C*-methyl (up) substitution pattern. Motivation or guidance to a person skilled to select an arbitrary hypothetical compound to further modify the same at 2'position as argued by the opponent is to be analyzed in view of the teachings of the other prior art documents as well.

92. From Park et al. I note that fluorine substitution can result into complex effects on drug metabolism which may have implications for drug efficacy and/or drug safety. Park et al. provides examples of hepatotoxicity (e.g., halothane hepatitis), nephrotoxicity (e.g., from methoxyflurane), and enhanced carcinogenicity (e.g., from fluorine substitution at certain positions on 7-methyl-1, 2-benzanthracene). Park et al. also mentions instances in which replacement of a hydroxyl group with a fluorine atom resulted in a complete or significant loss of potency. In other words there is no clear guidance or teaching for effective fluorine substitution. In view of teachings in Park, a person skilled is required to undertake further experimentation and to keep

various factors in mind before adopting the path shown in park while looking to invent an anti-HCV medicine. In my view it is a general article dealing with the subject.

93. Pankiewicz discusses various fluorinated nucleosides, including nucleosides with fluorine at the 2' (including doubly fluorinated at 2'), 3', 4', and 5' positions. It is a review article. I could not find any teachings for nucleosides having substitution pattern 2'-fluoro (down)-2'-methyl (up) substitution in Pankiewicz. Pankiewicz also states that introduction of fluorine atom into components of nucleic acids in general and nucleosides in particular frequently leads to a dramatic change in their biological activity and fluorine seriously affects stereoelectronic properties of the molecule. Pankiewicz teaches fluorination of primary and secondary carbons. I note the following statement in this article:

> *"direct nucleophilic displacement of a good leaving group in the 2'-ribo configuration with fluorine has been considered to be difficult, if not impossible …"*

The arguments of unpredictability of Applicant seems justified in view of this article. In my opinion Pankiewicz would have provided clear guidance to a person skilled for the claimed modification.

94. Opponents relied upon scheme 2 of the Wachtmeister et al. However, I could not find fluorination at 2' position of the sugar/nucleoside in the said scheme. This article discusses the synthesis of 4-substituted carbocyclic 2, 3-dideoxy-3-C-hydroxymethyl nucleoside analogues. Applicant has argued that Wachtmeister et al. teaches that attempting DAST may provide a mixture of products and DAST is unpredictable. Intermediate 16 in Wachtmeister et al. is structurally very different from the claimed compounds (carbocyclic compound with an alcohol at the 4-position). There is no guidance to a person skilled to fluorinate pentose sugars with alcohols at the 2- or 2'-position from this article. Opponent contends that Hertel et al. taught how to make compounds with fluorine at the 2' (down) position specifically Hertel et al.'s Compound 8 and Compound 12. However, Hertel et al. is relevant for di-fluorination at the 2' position. There is no guidance for the substitution pattern as

claimed in Applicant's invention.

95. The nucleosides disclosed in Matsuda et al. do not have 2' (up) methyl and 2' (down) fluorine. There is also no teaching for this substitution pattern in this document. Opponents argued that Hayakawa et al. shows that DAST was commonly used for 2'- and 3'-deoxynucleosides. However, Hayakawa et al. discloses fluorination of mainly primary or secondary alcohol. Applicant had also highlighted unpredictability of DAST fluorination reactions from this document. I could not find merits in the arguments on bio-isoestere and replacement of hydroxyl with fluorine based upon Maybridge MedChem. Considering the complexities involved in drug development and drastic changes in the properties of a compound with slight/minor modifications, a person skilled would not try or adopt a synthetic route or path unless there is clear guidance for the same. The prior art articles relied upon by the opponents were available to even to the inventors of patents which have been cited in the present opposition. However, only the inventors of the present application could arrive the claimed substitution pattern which has resulted in remarkable properties.

96. The compounds of WO'121, WO'282, WO' 287, WO'691, US'587, etc. does not provide a clear guidance for the claimed substitution pattern. A person skilled would not be motivated to select a compound for further research from prior art unless the same is enabled or listed as a promising compound. Selecting a hypothetical compound from a markush formula of a prior art document would require some or little motivation. Opponent did not provide any reasons for selecting imaginary compound for inventive step analysis. Apart from, as discussed above there is no clear teachings in the prior art documents for a person skilled to arrive at a substitution pattern as claimed by the Applicant. Middleton, Singh and Shreeve, Lino et al., Steven Caroll, the articles discussed above and other documents referred to by the opponents contained teaching which are general in nature or are in relation to different substitution pattern. I agree with the Applicant that none of the document show fluorination of tertiary alcohol at 2' position of sugar or nucleoside. Further, unpredictability due to DAST has been reported in almost all the articles relied upon by the opponents. If the relevant teachings as on the priority date of the present application are to be analyzed it appears that a skilled person would be aware that it

was known that structure activity relation relating to the anti-HCV activity of ribo-nucleosides are complex and fluorination in nucleosides would not always provide favorable results. Good amount of experimentations would have been required from the common general knowledge available as on the priority before a person skilled could have arrived at the claimed compounds. I find claimed invention inventive and non-obvious.

97. Accordingly, the ground for lack of inventive step is rejected.

SECTION 25(1)(F)- NOT PATENTABLE UNDER SECTION 3(D).

Submissions and arguments of Optimus, India Cares & Sankalp on Section 3(d) are as follows:

98. These Opponents argued that WO '121 and WO '282, disclose compounds which are known substances for the purpose of Section 3(d). They stated that in view of the compounds disclosed in the said prior art documents, claimed compounds are not patentable under Section 3(d). Referring to WO '121 and WO '282, attorney for the opponents argued that the compounds disclosed in the WO '121 and WO '282 the orientation of the fluorine the 2' position is in the 'up' position and methyl is at the 'down' position. Only difference from the claimed compounds is that the fluorine at the 2' position is in the 'down' position and methyl is in the 'up' position. The Opponents in their written note of submissions have contended that it is not necessary for Section 3(d) that that the known substance/compounds should 'exist' physically. Opponents have also stated that ordinary dictionary meaning of Existence is “n. the fact or; state of existing, a way of living. (in certain beliefs) any of person's successive early lives or archaic a being or entity. Further, the ordinary dictionary meaning of 'known' is “recognized, familiar, or within the scope or knowledge publicly acknowledged to be.

99. In the opposition petition these opponents have argued that the claimed compound should be therapeutically efficacious vis-à-vis Nucleoside analogues having 2’ methyl (up) and 2’ hydroxyl (down) as covered in the cited prior art documents such as WO’121, WO’282, WO’425, etc.

Submissions and arguments of DNP and IMAK on Section 3(d) are as follows:

100. Attorney for these opponents argued that WO'425 has shown various nucleoside analogs compounds including cytidine and uridine derivatives and their prodrugs having anti-HCV activity. It was argued that these compounds constitute the "known substance". Opponents argued that, the exemplified compounds of WO '425 are having same substitution pattern as disclosed in the impugned patent application. It was argued that the substitution at the 2' position with methyl group in the up configuration and a hydroxyl group in the down configuration is disclosed in WO'425 with cytidine as a base. Accordingly, opponents argued that compounds of impugned Claims 1-16 are derivatives of the compounds disclosed in WO'425 i.e. known substances.

101. Opponents also argued that the Applicant had made no attempt to provide the data for the 2' substituted uridine analog in their reply. They argued that the argument of Applicant that cytidine analog is getting converted into uridine analog in the body by a process of deamination should not be accepted. Opponent also argued that paper by the inventor of the' 6087 molecule i.e. Clark *et al* states uridine derivative demonstrated no anti-HCV activity or cytotoxicity in any assay and this should be treated as an admission in law.

Submissions and arguments of BDR on Section 3(d) are as follows:

102. Opponent BDR argued that Example 15 of Publication *"Matsuda et al"* involves the same substitution pattern with the methyl group in the up configuration and a hydroxy group in the down configuration with cytidine as a base and this constitute the "known substance". Opponent argued that the Applicant has failed to show any data in their specification showing greater therapeutic efficacy of the '6087 compounds over' the known nucleoside analogs in the prior art. Accordingly, Claims 1-14 of the impugned patent application '6087 should not be considered patentable and ought to be rejected. BDR has also argued that Clark *et al* states uridine derivative demonstrated no anti-HCV activity or cytotoxicity in any assay.

APPLICANT SUBMISSIONS WITH RESPECT TO SECTION 3(d).

103. Applicant argued that the Opponent (Sankalp) identified a nucleoside with pyrimidine base and methyl up and hydroxyl down at 2' position of nucleoside as the known substance. However, other Opponents did not identify any particular compound as the known substance from the prior art documents rather they argued that the entire class of compounds which are nucleosides and are either;

i. Methyl at the 2'position;

ii. Fluorine at the 2' position;

iii. Fluorine at the up and down at 2' position;

iv. Methyl at the up and down at 2' position; and

v. Methyl at the 2' up position and Hydroxy at 2' down position constituted the class of "known substance".

104. Applicant argued that Section 3(d) requires;

a. Identification of "..**a..**" known substance and not a class of substances;

b. If Section 3(d) applies, enhancement of efficacy was to be compared with "..**a..**" known substance and not against the class of compounds.

Applicant stated that the provisions of Section 3(d) are extremely clear on the language employed both in the main part of the section and in the explanation which use the word 'substance' in singular and not in plural. The Applicant submitted that the words "other derivatives" ought to be interpreted *ejusdem generis* and every new compound cannot be treated as a

derivative of any earlier compound. It is only new forms of compounds which are derived from the same known compound or the substance i.e. a new form of a known entity (Section 2(ta)) that would attract the rigors of Section 3(d). Applicant also stated that the present invention cannot be held to be a "mere discovery" within the meaning of Sec. 3(d).

Applicant stated that compounds of the present invention constitute New Chemical Entities (NCEs) and that the provisions of Section 3(d) are not applicable in the present case.

105. Applicant argued that presently claimed compounds have a unique and novel 2'-fluoro (down)–2'-methyl (up) substitution pattern, and they have both high potency and low toxicity as compared to compounds existed on the priority date. Applicant referred to the comparative efficacy data provided in the complete specification (Tables 1-9). The comparative activity shown in the said Tables includes efficacy and toxicity data against two 2'methyl up, hydroxyl down compounds i.e. 2'-C-methylcytidine and 2'-C-methyladenosine.

Case laws relied upon by the parties:

106. Opponent and Applicant, both have referred identical case laws which are followings:

i. Novartis Vs. Union of India (AIR 2013 SC 1311);

ii. F. Hoffman la Roche Ltd and Anr. Vs. Cipla RFA (OS) 92/2012

and RFA (OS) 103/2012, Para 62

ANALYSIS ON SECTION 3(d)

107. Both the sides have made elaborate arguments on the aspect as to what should be the known substance. Applicant has also emphasized that claimed compounds are new chemical entity and are not the derivatives.

Nucleosides and Nucleoside analogues were known in the prior art. Any further research or new invention in this field will obviously include the basic structure of nucleoside i.e. a base and a sugar. Thus, there is bound to be similarity in the core structure of new nucleosides analogues with the prior art or known nucleosides. However, to my mind, this should not be understood as structure similarity in this field of chemistry. Even if it is assumed that claimed compounds should be taken as structurally similar, then the issue could be what would be the known substance against which Applicant should have shown enhanced therapeutic efficacy.

Except the compounds highlighted in the opposition petition of Sankalp, the compounds argued to be known substance for this case are hypothetical in nature. None of such compounds in WO'121 and WO'282 are either exemplified or claimed. Further, opponents have not shown how a person skilled in art can make such hypothetical compounds from the teachings of the said patents. The synthetic routes prescribed in those patents may not lead to the compounds which are argued as the known compounds vis-à-vis

claimed compound. In other words, the suggested hypothetical compounds can only be thought of in view of Applicant's invention. An Applicant for patent cannot be required to make a compound which was not in existence as on the priority for showing comparative activities.

Further I note that Applicant has provided comparative activity and toxicity data via-a-vis compounds having 2'methyl up, hydroxyl down substitutions i.e. 2'-C-methylcytidine and 2'-C-methyladenosine. Opponents have also highlighted that structurally similar compounds are nucleosides having 2'methyl up and 2' hydroxyl down substitution pattern. Applicant has also argued that medicine made out of the claimed compounds have shown excellent efficacy as against all the known medicine for HCV. Applicant has argued that in fact this medicine is a complete cure for HCV and has also reduced the duration of HCV treatment.

Claimed compounds are not polymorphs, isomers, salts, etc. of a known compound. It is difficult to accept the contention of the opponents that the claimed compounds are derivatives of the known nucleosides especially when most of the indicated compounds of prior arts are not exemplified with known activity in the respective patents. Further, claimed compounds having 2' methyl (up) and 2' fluorine (down) with pyrimidine base cannot be considered as derived from or derivative of known compounds having 2' methyl (up) and 2' hydroxyl (down) with pyrimidine base. The process for

preparation of claimed compounds provided in the impugned application shows that claimed compounds are not derived from compounds having 2' methyl (up) and 2' hydroxyl (down). Further, the reliance upon article of Clark of the year 2005 is not relevant for the present analysis.

In the Novartis case, it has been held that efficacy means 'the ability to produce a desired or intended result'. Hence, the test of efficacy in the context of section 3(d) would be different depending upon the result the product under consideration is desired or intended to produce. In other words, the test of efficacy would depend upon the function, ability of the purpose of the product under consideration. Therefore, in the case of a medicine that claims to cure decease, the test of efficacy can only be "therapeutic efficacy". The Supreme Court in the said case has held that "therapeutic efficacy of a medicine must be judged strictly and narrowly". Supreme Court has also observed that the explanation to Section 3(d) requires the derivative to 'differ' significantly in properties with regard to efficacy'. What is evident therefore is that not advantageous or beneficial properties, but only such properties that directly relate to efficacy, which in case of medicine, as seen above, is its therapeutic efficacy. Applicant has shown the differences of their case from Novartis case in a tabulated form.

Further, decision in F. Hoffman La Roche lays down that section 3(d) assumes that structurally similar derivatives of a known 'substance' will also be functionally similar and hence ought not to be patentable. What is of critical importance is that this is not a provision that merely bars certain subject matter from patentability, on the contrary it provides that if the new form of the known substance is formed despite structural similarity to demonstrate a better functionality, it would qualify for assessment under Section 2(1)(j) as if it were a new product involving an inventive step and it would thereafter be up to the applicant for the patent to demonstrate the patentability of the substance in accordance with sections 2(1)(j) and (ja). It has further been observed that discovery of an entity or substance may not involve an inventive step. Insofar as there is no inventive step involved in its formation, it is merely a substance even though its structural form may be hitherto unknown. A new chemical entity (NCE) that is structurally dissimilar but functionally similar to an existing chemical entity is thus merely a substance under section 3(d). If the substance has an added layer of enhanced efficacy, then it will be treated as a 'new product' and would be eligible for assessment under Section 2(1) (j) to ascertain whether its formation involved an inventive step. If the new product involved one or more inventive step, then it will qualify as a pharmaceutical substance.

The patent application provides comparative activity and toxicity data in mice and monkey. Further, additional comparative activity data has been filed during the examination of the patent application. These data have been relied during the hearing. Further, Applicant also argued that the medicine prepared from the compounds claimed in the present invention has resulted in breakthrough treatment of HCV infection and the medicine is approved in many countries including USA and India. I am satisfied that claimed compound have added layer of enhanced efficacy.

From the above, it is clear that claimed compounds are outside the prohibition of Section 3(d). As stated earlier claimed compounds are novel and inventive.

108. Opponents DNP+, IMAK AND BDR have also submitted in their written notes of arguments that claimed compounds are not sufficiently and clearly described in the description of the patent application. However, no reason has been provided in this regard. I have looked into the description in detail. I find that the invention including the claimed compounds are sufficiently described and enabled in the patent specification. I note that Applicant has provided examples, schemes of synthesis, experimental data, figures and comparative activity and toxicity data. A person skilled in art will able to perform the invention in view of the description of the patent application.

I do not find any merit in relation to ground of Section 8. In fact, this ground was not argued during the oral hearing. However, this is captured in the written note of arguments filed by IMAK, DNP+ and BDR Pharma.

CONCLUSION:

109. In view of all above mentioned detailed discussion in the light of all the submissions of all opponents and applicant; and arguments before hearing by the applicant and all Opponents, the facts given in the documents submitted by all the parties, the all pre-grant representations are hereby dismissed. I find claimed compounds are novel, inventive and patentable under Patents Act. Accordingly, the instant application is allowed to proceed for grant with finally amended claims 1 to 8 as filed on 29th April, 2016 by the applicant.

110. There is no order as to the costs.

Dated this 9th May, 2016

(Dr.Rajesh Dixit)
Deputy Controller of Patents & Designs

Copy to:

1. **K&S PARTNERS** (Attorneys for the Applicant)
2. LAWYER Collective group (Opponents for Optimus, India Cares, Sankalp)
3. Fidus Law Chambers (Opponents for DNP+, IMAK AND BDR)