BEFORE THE CONTROLLER OF PATENTS,
THE PATENT OFFICE, MUMBAI

IN THE MATTER OF A PRE-GRANT OPPOSITION UNDER SECTION 25

And

IN THE MATTER OF PATENT APPLICATION NO. 201627039572 DATED
NOVEMBER 21, 2016 TITLED SOLID FORMS OF AN ANTIVIRAL
COMPOUND IN THE NAME OF GILEAD PHARMASSET, LLC. 333
LAKESIDE DRIVE, POSTER CITY, CALIFORNIA, 94404, U.S.A.

.....APPLICANT

And

IN THE MATTER OF REPRESENTATION BY WAY OF NOTICE OF
OPPOSITION FILED BY THE DELHI NETWORK OF POSITIVE
PEOPLE (DNP+)) .....OPPONENT

REPRESENTATION BY WAY OF OPPOSITION U/S 25(1)

1. A pre-grant opposition under Section 25(1) of the Patents Act, 1970, is herein
submitted by the Opponent against Indian Patent Application No.
201627039572 (hereinafter the “Present Application”) filed by Gilead
Pharmasset LLC (hereinafter the “Applicant”).

OPPONENT’S LOCUS STANDI

2. The Opponent, Delhi Network of Positive People (DNP+), is a community
based non-profit organisation representing the needs of people living
with HIV/AIDS (PLHIV) and Hepatitis C (HCV), and is registered as a Trust
with its registered address at Flat no. A1-5, Property 141 Gali No. 3, Harijan
Colony, Neb Sarai, New Delhi, 110068.
3. The Opponent is a network working extensively in the area of access to medicines. Its work includes but is not limited to service delivery, treatment literacy and community empowerment. The main focus is advocating for access to medicines as it believes every individual should get treatment and no one should suffer due to lack of medicines. Of the main concerns to the Opponent, is the impact of product patent on access to affordable Hepatitis C medicines for people not just in India but across the developing world.

4. Section 25(1) of the Patents Act allows any person, to represent an opposition against grant of a patent. Therefore, the Opponent has the locus standi to make this representation against grant of patent.

**BACKGROUND OF HEPATITIS C**

5. According to World Health Organisation (WHO) Global Hepatitis Report, 2017 an estimated 325 million people worldwide are living with chronic Hepatitis B or C virus infection. The report indicates that 71 million people are estimated to be living with chronic Hepatitis C infection with majority of them with limited access to life saving HCV testing and treatment. Increasing mortality rates due to Hepatitis C infection when compared with HIV and Tuberculosis deaths is a cause of concern. In 2016, viral hepatitis caused 1.34 million deaths.¹

6. Hepatitis C is a blood borne virus. The infection spreads from exposure to infected blood during unsafe injection practice, injecting drug use, transfusion of unscreened and unsafe blood products and in unsafe health care. In India, a rough estimate indicates there are 10 to 15 million chronic carriers of HCV², absence of a surveillance system to track HCV infection in India and presence of PLHIV community with undetected HCV co-infection further necessitates

the need for early access to care and treatment. Though Hepatitis C is red flagged as a major public health concern and termed as a ticking time bomb by the WHO, access to treatment and medicines continues to be abysmally low for people with hepatitis C infection. Of the many obstacles in access to HCV medicines, patent protection leading to high cost of medicines poses to be a major barrier in accessing affordable HCV medicines.

7. In the 1990s, the phosphoprotein non-structural protein 5A (hereinafter referred to as “NS5A”) was widely investigated. By the late 1990s, NS5A had also been identified as exhibiting a role in cell growth regulation [Ghosh, et al., “Hepatitis C virus NS5A protein modulates cell cycle regulatory genes and promotes cell growth” (1999) Journal of General Virology 80(5):1179–83]. NS5A inhibitors block a virus protein, NS5A, that Hepatitis C Virus (HCV) needs to reproduce and for various stages of infection. Velpatasvir is a NS5A inhibitor in the Direct-Acting Antiviral (DAA) category. The other known NS5A inhibitors include Ledipasvir, Sofosbuvir and Daclatasvir.

**THE PRESENT APPLICATION**

8. As per the information available on INPASS, the Present Application was filed by Gilead Pharmasett LLC (Applicant) at the Patent Office on 21.11.2016 with 80 claims. The Present Application is a PCT national phase application of Application No. PCT/US2015/034649 dated 08.06.2015. The Present Application claims priority dated of 11.06.2014 from US Patent Application No. US 62/010,919.

9. The Applicant made a request for examination on 21.11.2016. Till the date of filing of this opposition, no examination report has been issued.

10. The Present Application seeks to patent a compound which used is to treat Hepatitis C.

11. It is the Applicant’s case that side effects of known drugs targeting the liver limit their usefulness (see running page 1 of the complete specification, “Background”). However, the Applicant fails to indicate how the alleged invention in the present application overcomes this side effect.
THE ALLEGED INVENTION

12. The Present Application purportedly discloses and claims crystalline solid forms, its salts, co-crystals, hydrates and solvates of \((2S)-1-\{(2S,5S)-2-(9-\{2-(2S,4S)-1-\{(2R)-2[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl\}-1,1\text{-dihydroisochromena[4',3':6,7]naptho[1,2-d]imidazole-2-yl}\}-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl\}carbamate as reproduced below:

![Compound I](image)

13. It is the Applicant’s case that the Present Applicant discloses the process of making this compound and its therapeutic methods of use.

14. The Applicant has admitted in the complete specification that Compound I (as disclosed above) is known to exhibit anti-viral properties and can be synthesized according to the methods described in WO 2013/075029 (see complete specific at internal page 1, last paragraph).

15. The Present application claims various crystalline forms of Compound I, crystalline forms of bis-hydrochloride salt of Compound I, crystalline forms of phosphate of Compound I, Crystalline form of L-Tartrate of Compound I, Crystalline form of D-Tartrate of Compound I.

CLAIM CHART

16. The 80 product claims can be divided into following 20 groups. That is, the Present Application seeks to claim 20 crystalline forms of a known substance - Velpatasvir and Velpatasvir salts/co-crystals.

<table>
<thead>
<tr>
<th>Coverage</th>
<th>Claim numbers</th>
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<tbody>
<tr>
<td>Compound I Form I</td>
<td>1-5</td>
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</table>
17. It is submitted that a review of the priority application US 62/010, 919 (hereinafter “US ’919”) reveals that compound of claims 79-80 have not been disclosed therein.

18. There are various portions in the Present Application which were not disclosed in US ’919 on the basis of which priority is claimed. In this regard, attention is drawn to last paragraph at internal page 8, starting with “Some embodiments provided herein...” ending on internal page 9, at paragraph 3 at “…on a diffractometer using Cu-Kα radiation at a wavelength of 1.5406 Å.” Further, attention is drawn to internal page 12 of the Present Application at “Fig 50 shows...” to internal page 13 at, “FIG.53 shows a dynamic vapour sorption (DVS) curve of compound I D-tartate Form II”. Attention is also drawn to internal page 15 of the Present Application at paragraph 3, “The D-tartrate complex of Compound I...Compound I D-tartrate Form I and Compound I D-tartrate Form II.”. These features in the Present Application and what is stated in section 2.5 on internal page 47 of the Present

<table>
<thead>
<tr>
<th>Compound</th>
<th>Form</th>
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<tbody>
<tr>
<td>Compound I bis-hydrochloride Form II</td>
<td>6-10</td>
<td></td>
</tr>
<tr>
<td>Compound I bis-hydrochloride Form III</td>
<td>11-15</td>
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<td>Compound I bis-hydrochloride Form IV</td>
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<td>Compound I bis-hydrochloride Form V</td>
<td>21-25</td>
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<tr>
<td>Compound I bis-hydrochloride Form VI</td>
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<tr>
<td>Compound I Phosphate Form VII</td>
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<td>Compound I Phosphate Form VIII</td>
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<td>Compound I Phosphate Form IX</td>
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<td>60-62</td>
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<tr>
<td>Compound I Phosphate Form XV</td>
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<td>Compound I L-Tartrate Form XVI</td>
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<td>Compound IL-tartrate Form XVII</td>
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<td>74-78</td>
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<td>Compound ID-tartrate Form I</td>
<td>79</td>
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<tr>
<td>Compound ID-tartrate Form II</td>
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</table>
Application were not disclosed in the priority applicationUS '919. Therefore, claims 79-80 cannot claim a priority date of 11.06.2018.

SUMMARY OF GROUNDS CONSIDERED FOR OPPOSITION

19. The Opponent brings this opposition under the following grounds, amongst others, each of which are without prejudice to one another:

i. Claims 1-80 the Present Application lack inventive step, and fail under Sections 2(1)(j) and 2(1)(ja) of the Patents Act, 1970. Therefore, the Opponent brings this opposition under Section 25(1)(e)-that the invention claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published before the priority date in India or elsewhere in any document.

ii. Claims 1-80 of the Present Application do not satisfy the test of Section 3(d) of the Patents Act, 1970 as the subject matter does not exhibit enhanced therapeutic efficacy. Therefore, the Opponent brings this opposition under Section 25(1) (f) -that the subject of any claim of the complete specification is not an invention within the meaning of this Act.

iii. The Opponent brings this opposition under Section 25(1) (h) of the Act-viz. that the Patent Applicant has failed to disclose the information required by Section 8.

DETAILED GROUNDS

I. CLAIMS 1 TO 80 ARE OBVIOUS, DO NOT INVOLVE A TECHNICAL ADVANCE AND LACK INVENTIVE STEP AS DEFINED UNDER SECTION 2(1)(ja) AND THEREFORE HAVE TO BE REJECTED UNDER SECTION 25(1)(e)

20. Section 2(1) (j) defines an “invention” as “a new product or process involving an inventive step and capable of industrial application.” For an alleged invention to qualify for a patent, it must satisfy the criteria of inventive step. Section 2(1)(ja) of the Patents Act defines an inventive step as “a feature of an invention that involves technical advance as compared to the existing
knowledge ... and that makes the invention not obvious to a person skilled in the art”.

21. Thus a Patent Applicant is required to show that the feature of the alleged invention involves a technical advance and is not obvious to a person skilled in the art (POSITA).

22. For raising a ground under Section 25(1)(e), the published matter to be considered may include matter published in India or elsewhere in any document before the priority date of the alleged invention. The Opponent submits that claims 1-80 of the Present Application lack an inventive step and therefore should be rejected.

23. On the priority date of the alleged invention, as will be explained below, the following were well known to persons skilled in the art:

i. The compound - methyl \( (2S) - 1 - \{(2S,5S) - 2 - (9 - \{2[(2S,4S) - 1 \{(2R) - 2 - [(methoxycarbonyl)amino] - 2 - phenylacetyl}\} - 4 - (methoxymethyl)pyrrolidin - 2 - yl]\} - 1H - imidazol - 5 - yl\} - 1,11 - dihydroschromeno[4',3':6,7]napthol[1,2-d]imidazole - 2 - yl\} - 5 - methylpyrrolidin - 1 - yl\} - 3 - methyl - 1 - oxobutan - 2 - yl\} carbamate;  

ii. Salt selection for developing optimal drug candidate was routine practice in drug industry;

iii. Investigation of polymorphism of known compounds as routine practice in pharmaceutical industry;

iv. Crystalline forms of salts of existing DAAs were known.

i. The compound - methyl \( (2S) - 1 - \{(2S,5S) - 2 - (9 - \{2[(2S,4S) - 1 \{(2R) - 2 - [(methoxycarbonyl)amino] - 2 - phenylacetyl}\} - 4 - (methoxymethyl)pyrrolidin - 2 - yl\} - 1H - imidazol - 5 - yl\} - 1,11 - dihydroschromeno[4',3':6,7]napthol[1,2-d]imidazole - 2 - yl\} - 5 - methylpyrrolidin - 1 - yl\} - 3 - methyl - 1 - oxobutan - 2 - yl\} carbamate, was known as on the priority date of the Present Application.
24. The Opponent relies on patent publication no. WO 2013/075029 A1 (hereinafter “WO ’029” and annexed hereto as Exhibit A) titled, “Condensed Imidazolylimidazole as antiviral compounds” published on 23.05.2013. Given that this document has been published before the date of priority, viz. 11.06.2014, this publication can be relied on as prior art for the Present Application. The publication discloses a compound for use as HCV therapeutic agent.

25. WO ’029 discloses “a pharmaceutical composition for use in treating hepatitis C(HCV).” (See running page 26 at lines 17-19 of WO ’029). WO ’029 discloses a compound, the Markush structure of which is reproduced hereinbelow (see running page 25 at Exhibit A)

![Formula I]

26. Attention is drawn in particular to running page 231 at WO ’029 wherein Example PY discloses the process for synthesizing the following compound:

![Formula I]

27. It is submitted that the process for synthesizing this compound has been described in detail therein. WO ’029 in this regard states, “A solution of tert-butyl(2S,4S)-2-[5-(2-[(2S,5S)-1[N-(methoxycarbonyl)-L-valyl]-5]methylpyrrolidin-2-yl]-1H-imidazol-5-yl]-1,11-dihydroisochromeno[4',3':6,7]naptho[1,2-
[imidazole-9-yl]-1H-imidazol-2-yl]-4-(methoxymethyl)pyrrolidine-1-carboxylate (150 mg, 0.19 nmol) in 1.25 N HCl in EtOH(3 mL) was stirred overnight then heated to 50°C for 3h. The reaction was concentrated and the crude material dissolved in DMF (2 mL). To this solution was added a solution of ₴-2-(methoxycarbonylamino)-2-phenylacetic acid (52 mg, 0.25 nmol) and COMU (90 mg, 0.21 nmol). To the resulting solution was added diisopropylethylamine (0.099 mL, 0.57 nmol). After stirring for 2h at room temperature, the reaction was quenched with 1N HCl (0.2000 mL) and purified by HPLC. After lyophilisation, the TFA salt was dissolved in EtOAc and washed with saturated NaHCO₃. The organic phase was dried over Na₂SO₄ and concentrated. The free base was then dissolved in MeCN/H₂O and lyophilized to afford methyl {(2S)-1-{[(2S,5S)-2-(9-{2-[{(2S,4S)-1-{(2R)-2-[(methoxycarbonylamino)-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl]-2,11-dihydroisochromeno[4',3':6,7]napthol[1,2-d]imidazole-2-yl]-4-(methoxymethyl)pyrrolidin-2-yl]carbamate (65 mg, 39%). LCMS-ESI: calculated for C₄₉H₅₄N₈O₈:882.4; observed [M+1]⁺: 884.1. Diagnostic peaks in NMR 'H NMR (CD₃OD): 8.28 (s,1H), 8.21 (s, 1H), 8.04 (s,1H), 7.91-7.01 (m,10H), 3.62 (s,3H), 3.34 (s,3H), 3.23 (s,3H), 1.56 (d,3H), 1.03 (d,3H), 0.94 (d,3H).” (see Exhibit A, running pages 231-232 of this representation).

28. It is submitted that the example not only exemplifies the production but also the NMR values of the product so obtained.

29. Attention is also drawn to the claims of WO ’029. It is submitted that one of the compounds claimed in claim 22, in particular the second compound is depicted as following:
30. Further, claim 23 of WO '029 claims pharmaceutically acceptable salt or prodrug of the above disclosed compound (see running page 270 at Exhibit A). As per the complete specification of WO '029 it also includes the pharmaceutically acceptable salt of the disclosed compound (see running page 26 at placitum 13-16). It inter alia discloses salts of inorganic acid of the disclosed compound, namely, hydrochloric, sulfuric, phosphoric and sulphamic (see Exhibit A, running page 37 at paragraph 4, running page 37 at paragraph 1). Further, the WO '029 discloses how the salts of the disclosed compound may be made. It states that, “In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g. HCl, HBr, H₂SO₄, H₃PO₄ or organic sulfonic acids, to basic centers, typically amines, or to acidic groups.” (emphasis supplied) (see Exhibit A at running page 37 at placitum 15-19).

31. Similarly, claim 24 of WO '029 claims pharmaceutically acceptable salt or prodrug of compound of Formula I (disclosed above) and claim 40 claims their use in prophylactic or therapeutic treatment of hepatitis C or Hepatitis C associated disorder.

32. Therefore, a POSITA, working on Hepatitis C inhibitor, on reading WO '029 would be motivated to further work on the compounds disclosed therein. Further, a POSITA would be motivated to explore the characteristics of the disclosed compounds, in particular claimed compounds as that in Figure I. From the disclosure in the specification of WO '029, it is also clear that Hydrochloric or Phosphoric salts of the disclosed compounds could be made.

ii. Salt selection for developing optimal drug candidate was routine practice in drug industry before the priority date of the Present Application

Gould et al (Published: 1986)

33. The Opponent relies on a publication authored by Gould et al, titled “Salt selection for basic drugs”, published in 1986, (hereinafter “Gould et al”, a copy of which is hereto annexed and marked as Exhibit B).
34. Gould et al described a rationale for salt selection, and that the selection is based on physicochemical properties, melting point, solubility, stability, wettability and hydrophobicity of various salt forms. Gould et al also listed various salt candidates that could be prepared.

35. Gould et al notes, “Clearly, issues exist for rejecting certain salt forms, but generally a plethora of conjugate acids may still be available for exploitation. To assist this selection details of a wide series of conjugate acids including details on structure, melting point, pK<sub>a</sub>, LD<sub>50</sub>, and examples of use are provided in the appendix. On occasions, there appears some rationale for investigating non-standard salt forms, as opportunities for correcting or addressing a specific problem of the drug substance in its target dosage form.” (See conclusion at running page 289 at Exhibit B).

Morris et al (Published: 1994)

36. The Opponent relies on a publication authored by Morris, et al, titled “An integrated approach to the selection of optimal salt form for a new drug candidate”, published in 1994 (hereinafter referred to as “Morris et al”), and a copy of which is hereto annexed and marked as Exhibit C). Morris et al was published in 1994, much before the priority date of the Present Application viz. 11.06.2014. Hence Morris et al can be relied upon as a prior art for the purposes of the Present Application.

37. Morris et al described a tiered salt selection process that could be completed in four to six weeks to determine the optimal salt form of a compound. It notes that, “The number of tiers necessary to reach a decision on the optimal salt form of a compound may depend on the physicochemical properties studied and the number of salts available. This salt selection process can be completed within 4-6 weeks and be easily adopted in the drug development program” (See lines 19-21 of the abstract of Exhibit C at running page 294 of the representation).

38. Morris et al elucidated that all salt forms of the selected compound which were found to be crystalline were tested at tier 1 for their hygroscopicity(See
RHS column, lines 33-36 at running page 295 at Exhibit C). The salts which were considered to have acceptable hygroscopicity were then screened in tier 2 for changes in crystal structure by using combinations of powder X-ray diffraction and thermal analysis techniques. (See LHS column at lines 11-16 at running page 296 at Exhibit C). Further, “at tier 3, the selected salts were subjected to accelerated thermal stability and photostability screening.” (See LHS column, para 3, lines 44-46 at running page 296 at Exhibit C).

Serajuddin et al (Published: 2002)

39. Opponent relies on a chapter authored by Abu T. M. Serajuddin and Madhu Pudipeddi titled, “Salt Selection Strategies”, in the P. Heinrich Stahl and Camille Georges Wermuth (eds.), Handbook of Pharmaceutical Salts: Properties, Selection and Use (2002), IUPAC, Chapter 6, pp.135–160,(hereinafter “Serajuddin et al”, a copy of which annexed hereto and marked as Exhibit D). Serajuddin et al was published in 2002, much before the priority date of the present application viz. 11.06.2014. Hence Serajuddin et al can be relied upon as a prior art for the purposes of the Present Application.

40. Serajuddin et al notes that “The salt selection should be viewed as a part of the overall objective of selecting the ‘optimal form’ of a drug candidate for development. When one refers to the optimal form, it involves both chemical and physical forms. A new chemical entity can be acid, a base, or neutral species. If it is a neutral species, there are no options for chemical manipulation to make it more developable other than possibly preparing prodrugs. On the other hand, if it is an acid, or a base, one can select the free acid or base form, or, alternatively, one can select salt form.” (See Exhibit D at running pages 305 at lines 19-26). It further notes that, “Along with the evaluation of chemical form, the strategy for the selection of physical form must also be considered. One needs to determine whether the compound exists in crystalline or amorphous form, and if crystalline, whether it exhibits polymorphism.” (See Exhibit D at running pages 305 at lines 32-35).
41. Serajuddin et al further described a multitier approach to screen salts for their optimal physical form. It notes that Tier 1 includes examining crystallinity of salts by simple visual or microscopic method. If the results of visual and microscopic examinations are inconclusive, powder X-ray diffraction may be used. If a particular salt is found to be noncrystalline, attempts are made to crystallize it from alternate solvents. In many cases, more than one solvent is tried for the crystallization of drugs. Based on these studies salts are deemed to have acceptable crystallinity and aqueous solubility elevated to Tier 2. In Tier 2, an in-depth characterization of crystal properties are conducted by using such techniques as powder X-ray diffraction, hot stage microscopy, differential scanning calorimetry, thermal gravimetric study, and so forth (See Exhibit D at running pages 323-324). Below is a flow-chart explaining tiered approach disclosed in Serajuddin et al.

![Tiered Approach Flowchart]

42. Therefore, a POSITA on reading Gould et al, Morris et al and Serajuddin et al, working on DAAs would be motivated to explore salt forms of known DAAs and investigating whether the compound exists in crystalline or amorphous forms.
iii. Investigation of polymorphism of known compounds was routine practice, before the priority date of the Present Application

Laszlo Borka et al (Published: 1990)

43. The Opponent relies on a publication authored by Laszlo Borka et al titled “Crystal Polymorphism of Pharmaceuticals”, Acta Pharmacutica Jugoslavica 40 (1990)71-94 (hereinafter “Borka et al”, marked and annexed as Exhibit E). Given that this article was published in 1990, before the priority date of the present application viz. 11.06.2014, it can be relied on as a prior art for the purposes of the Present Application.

44. Borka et al notes that, “Drug regulation documents submitted by leading pharmaceutical companies to regulatory bodies will today, almost without exception, have a section on polymorphism when describing the physico-chemical properties of the active substance.” (See Exhibit E at running page 330, at lines 14-17). The paper identifies several methods using which polymorphs can be identified, including infra-red spectroscopy, X-Ray Diffraction method, polarized light microscopy, thermo microscopy, Differential Scanning Calorimetry, Differential Thermal Analysis, Raman spectroscopy, solid state nuclear magnetic resonance (NMR) and cross spinning and magic-angle spinning techniques. (See Exhibit E at running page 331 at lines 6-38).

45. Borka et al further notes that, “On the other hand, X-ray diffraction methods on single crystals or powdered samples almost never fail due to their outstanding ability of detecting differences in crystal structures.” (See Exhibit E at running page 331 at lines 12-14).

46. Therefore, Borka et al shows that, as on the date of priority of the present applications, investigation of polymorphic forms of known pharmaceutical substances was routine practice in pharmaceutical industry. Various methods of identifying polymorphic forms of pharmaceutical substances were also known on the priority date of the present application.
**Mino R. Caira** (Published:1998)


48. *Caira* notes that, “Since the rate of transformation of metastable polymorphs to the stable one may be slow, it is quite common to encounter several polymorphs of a single compound under normal laboratory conditions. Organic compounds tend to form different polymorphs owing to weak, non-directional intermolecular interactions which exist in the solid state.” (See **Exhibit F** at running page 355 at lines 5-10).

49. *Caira* states that, “Systematic investigation of a compound to determine whether it is prone to polymorphism, as well as the nature of the polymorphism (enantiotropic or monotropic) [23], is routine practice in pharmaceutical pre-formulation studies. Identification of the different polymorphic forms of a drug substance, determination of their chemical and physical properties, thermodynamicstabilities, and temperatures and rates of interconversion are essential for ensuring drug preparations with reproducible behaviour [24]. Already, legislation requiring drug manufacturers to provide information relating to the occurrence (or apparent absence) of polymorphism in their products has been introduced [41]. Demonstrating the absence of a tendency to polymorphism is not easy; most substances when investigated for a sufficiently long time will reveal more than one polymorph [42].” (emphasis supplied) (See **Exhibit F** at running page 355 at lines 34-38 and page 165 at lines 1-7).

50. *Caira* also discusses the preparatory methods for polymorphs. It states, “Research on the polymorphism of a new molecular entity normally commences with experimental screening which can indicate the occurrence of
more than one crystalline form of the substance. An inexpensive method of such testing is hot stage microscopy (HSM), which has been used very extensively and effectively by a leading proponent [80] for many years to provide preliminary indications of the presence of crystalline polymorphic and pseudopolymorphic (solvated), as well as glassy (amorphous) forms, all of which may have practical utility.” (See Exhibit F at running page 368 at lines 8-14).

51. Further it notes that, “Once the existence of multiple forms is established, practical methods for the preparation of specific forms on a larger scale may be explored. Frequently, recrystallization of the compound from solvents or solvent mixtures spanning a wide polarity range is effective in producing several of the different forms in sufficient quantity for complete characterisation by the analytical methods to be discussed. Most pseudopolymorphs are prepared by crystallization of the parent organic compound from the respective solvent, whereupon the latter becomes incorporated in the new crystal.” (See Exhibit F running page 368 at lines 23-31).

52. Caira identifies several methods of preparing polymorphs, including, “Mechanical grinding and compression of compounds represent another possible route to polymorphs. In the former case, the local pressures induced by the mechanical stress may initiate the transformation of the original polymorph into another crystalline form. From an industrial viewpoint, grinding and compression are attractive processes, being relatively inexpensive and requiring no solvents.” (See Exhibit F at running page 369, last paragraph and page 179 at lines 1-4).

53. Hence, a reading of Caira makes it evidently clear that investigation of polymorphism of known compounds was a routine practice in the pharmaceutical industry on the date of priority of the present application.

54. Therefore, on reading Borka et al and Caira, a POSITA, working on DAAs, would be motivated to investigate polymorphic forms of known pharmaceutical substances.
iv. Crystalline forms of salts of existing Direct Acting Antivirals were known before the priority date of the Present Application

**WO2009020828** (Published: 12.02.2009)

55. It is submitted that as on the priority date of the Present Application, the salts of known DAAs such as Daclatasvir, Sofosbuvir and Ledipasvir were known.

56. In this regard, the Opponent relies on WO2009020828 titled “Crystalline form of methyl ((1s)-1-(((2s)-2-(5-(4'-(2-((2s)-1-((2s)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1h-imidazol-5-yl)-4-biphenylyl)-1h-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride salt” published on 12.02.2009 and filed by Bristol-Myers Squibb Company (hereinafter “WO ’828” and annexed as Exhibit G). It is submitted that WO ’828 relates to the drug commonly known as Daclatasvir.

57. The publication discloses that, it relates to “a crystalline form of methyl ((15)-l-(((25r)-2-(5-(4'-(2-(25r)-l-((25r)-2-((methoxycarbonyl)amino)-methylbutanoyl)-2-pyrrolidinyl)-lH-imidazol-5-yl)-4-biphenylyl)-lH-imidazol-2-yl)pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride salt.” Further, it discloses that the invention therein generally relates to “a pharmaceutical composition comprising a crystalline form, as well of methods of using a crystalline form in the treatment of Hepatitis C virus (HCV) and methods for obtaining such crystalline form.” (See running page 402 at placitum 11-23 at Exhibit G).

58. Further, WO ’828 discloses general methods of preparing crystals, including suspension of the compound a suitable solvent to afford a slurry (see running pages 410 to 412 at Exhibit G). Attention is drawn to claims 1-11 of WO ’828. They claim various crystalline dihydrochloride form of Daclatasvir. Hence, WO ’828 not only discloses a crystalline form of a known DAA but also a dihydrochloride salt thereof.

**WO2013184698** (Published: 12.12.2013)
59. The Opponent further relies on WO2013184698 titled “Solid Forms of an Antiviral Compound” published on 12.12.2013 (hereinafter “WO ’698” and annexed hereto as Exhibit H). It is submitted that WO ’698 was published before the priority date of the present application viz. 11.06.2014, hence qualifies as a prior art.

60. WO ’698 discloses crystalline form of Ledipasvir, identified as compound I in WO ’698. It further discloses that Ledipasvir acts as an anti-HCV agent(see para 002 at running page 448 at WO ’698, Exhibit H). It further discloses crystalline forms of Ledipasvir with specific X-Ray Diffraction peaks (see paras 006-022 at running pages 449-453 at Exhibit H).

61. In fact, WO ’698 claims crystalline forms of Ledipasvar with different X-Ray peaks at claims 1-73 (see running pages 519-526 of Exhibit H).

62. Therefore, on reading WO ’828 and WO ’698, a POSITA, working on DAA would be motivated to explore crystal forms of other known DAAs in the art.

63. A person skilled in art (POSITA) working on DAAs on reading WO 2013/075029 would be motivated to explore the compounds disclosed therein, including- methyl {(2S)-1-[((2S,5S)-2-((9-{2[(2S,4S)-1{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl})-1,11-dihydroisochromeno[4’,3’:6,7]napthol[1,2-d]imidazole-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate. On reading Gould et al, Morris et al, Serajuddinet al, a POSITA would be motivated to analyse salts of compounds disclosed in WO ’029. Further on reading Laszlo Borka et al and Mino R. Caira, a POSITA would be motivated to investigate whether the compounds disclosed in WO ’029 exhibited polymorphism. On reading WO2009020828 and WO2013184698, a POSITA would take note that other DAAs have shown polymorphism, and therefore would be motivated to explore other forms of compounds disclosed in WO ’029. On combining the teachings of these prior art documents, a POSITA would arrive at compounds claimed in Present Application.
II. That claims 1-80 of the Present Application do not satisfy the test of section 3(d) and therefore are objected to under section 25(1) (f)

64. Without prejudice to other grounds raised herein, it is submitted that claims 1-3 fail under section 3(d) of the Patents Act.

65. Section 3(d) of the Patents Act was amended in 2005 to prevent patents on modification of known substances. It is an established position of law that S. 3(d) has to be satisfied independently of Section 2(1)(j) and S. 2(1)(ja) [see Novartis AG versus Union of India and Others (2013) 6 SCC 1]. This requirement under S. 3(d) is to be satisfied by the Applicant by showing efficacy, which in case of pharmaceutical products will be therapeutic efficacy (see Novartis AG versus Union of India and Others 2007 4 MLJ 1153, para 13). Further, such data has to be provided by the Applicant in the complete specification (see the order of the Hon’ble IPAB, Novartis AG versus Union of India, MIPR 2009 (2) 0345, para 9(xvii)).

WO 2013/075029 (Published 23.05.2013)

66. The Opponent relies again on Exhibit A- WO ’029. As noted above, WO ’029 discloses Example PY discloses the process for synthesizing the following compound (See running page 231):

![Chemical Structure](Image)

Formula I

67. It is reiterated that, claim 23 of WO ’029 claims pharmaceutically acceptable salt or prodrug of the Formula I (see running page 270at Exhibit A). Further, as per the complete specification of WO ’029 the patent publication also
includes disclosed compound and its pharmaceutically acceptable salt thereof (see runningpage 26 at placitum 13-16). In particular, the it \textit{inter alia} discloses salts of inorganic acid of the disclosed compound, namely, hydrochloric, sulfuric, phosphoric and sulphamic (see Exhibit A at running page 37 at paragraph 4 and running page 38 at paragraph 1).

68. Therefore, it is submitted that compound of Formula I disclosed in WO ’029 is the closest compound to those claimed in the Present Application. Therefore, claims of the Present Application are mere derivatives of the compound disclosed in WO ’029. Below is a tabular representation of how claims of the present application are mere derivatives of the compound of Formula I of WO ’029.

<table>
<thead>
<tr>
<th>Claimsof the Present Application</th>
<th>Nature of derivative of Formula I in WO ’029</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-5</td>
<td>Crystalline form of Formula I</td>
</tr>
<tr>
<td>6-30</td>
<td>Crystalline form of bis-hydrochloride form of Formula I</td>
</tr>
<tr>
<td>31-65</td>
<td>Crystalline form of phosphate of Formula I</td>
</tr>
<tr>
<td>66-73</td>
<td>Crystalline form of L-tartrate of Formula I</td>
</tr>
<tr>
<td>74-78</td>
<td>Crystalline form of HBr salt of Formula I</td>
</tr>
<tr>
<td>79-80</td>
<td>Crystalline form of D-tartrate form of Formula I</td>
</tr>
</tbody>
</table>

69. It is clear from the above table that the claims of the Present Application are mere polymorph forms of bis-hydrochloride salt, or phosphate salt, or L tartrate salt, or HBr salt or D-tartrate salt of Formula I disclosed in WO ’029. The Applicant, however, has failed to provide any data that indicates that the compounds of claims 1-80 show an enhancement of therapeutic efficacy of compound of Formula I disclosed in WO ’029, which it was bound to show. Therefore, claims 1-80 must be rejected as they fail to comply with the standards laid down in S. 3(d).

III. That the Applicant failed to disclose information required by Section 8, hence the opposition is raised under Section 25(1)(h)

70. Section 25(1) (h) of the Patents Act provides a ground for opposition if the patent applicant has not furnished information required under Section 8 of the
Patents Act, within the time prescribed by law. Without prejudice to other grounds raised herein, the Present Application should be rejected because the Patent Applicant has not complied with the mandatory requirements of Section 8 of the Patents Act.

71. Section 8 of the Patents Act read with rule 12(1) of the Patents Rules requires, *inter alia*, a patent applicant, who is prosecuting, either alone or jointly with any other person, an application for a patent in any country outside India in respect of the same or substantially the same invention, to file a statement setting out the particulars of such application (Form -3) within six months of the date of filing of such application in India.

72. On 16.11.2017, the Applicant filed Form-3 giving details of the status of corresponding applications (of the Present Application) in other jurisdictions. This form indicates that apart from India, the corresponding application has been filed in Argentina, Australia, Brazil, Canada, People’s Republic of China, Eurasean Patent Organization, European Patent Convention, Hong Kong, Israel, Japan, Republic of Korea, Mexico, New Zealand, Singapore, Taiwan and United States of America.

73. It is submitted that the USPTO allowed patent grant to this application only after deletion of several claims. However, the Applicant has deliberately mentioned that the application was granted a patent and failed to indicate the amendments made to the claims.

74. Further, it is submitted that the Applicant has failed to inform the patent office that its application in Australia(AU2015274961) has lapsed.

75. It is further submitted that the Applicant has made amendments to the claims in applications covering similar invention filed in Canada and European Union. The Applicant however has chosen to not submit details related to amendment of claims and the objections related to obviousness, raised in the examination reports in different jurisdictions.

76. Given that complete information related to the corresponding applications in other jurisdictions hasnot been given, ground for opposition under S. 25(1) (h) of the Patents Act is raised. The Controller is requested to direct the
Applicant to submit translated copies of the opposition proceedings in these jurisdictions to facilitate examination of the Present Application.

PRAYER FOR RELIEF

In view of the above said references Opponent prays as follows:

a) To be heard and be allowed to lead evidence (documentary and oral) before any order is passed;

b) To reject the claims of 201627039572 filed by Gilead Pharmasset LLC *intoto*;

c) To allow the Opponent to file further documents as evidence if necessary to support the averments;

d) To allow amendment of the opposition as and when the need may arise;

e) To allow the Opponent to make further submissions in case the Applicant amends the claims;

f) For costs in this matter;

g) For any further and other relief in the facts and circumstances that may be granted in favour of the Opponent in the interest of justice.

Dated this the 9th day of July 2018

OPPONENT

To

The Controller,
The Patent Office Branch
MUMBAI