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By Hand Delivery

September 26, 2009

The Controller of Patents  
Patent Office,  
IP Building, Guindy Industrial Estate,  
Chennai 600032.

EDP  
MWS  
29/9/09

Kind Attn. Dr. S.P. Subramaniam  
Asst. Controller of Patents

Sirs,

Sub. Written Submissions of the Opponent - in Post-Grant opposition under S.25(2) of the Patents Act, 1970 in respect of Patent no.(207232)959/MAS/1995 – Patentee – F Hoffmann La Roche AG – Opponent – Delhi Network of Positive People (DNP+) - Reg.

With respect to the captioned subject in the post-grant opposition filed by the Delhi Network of Positive People, consequent to the hearing on 04.08.09 and while thanking you for the kind courtesies extended please find enclosed the Written Submissions being filed on behalf of the Opponents (DNP+).

You are requested to kindly take the above on record and oblige. A Copy of the same (also enclosed) may be forwarded to the Patentee. While so your requested to kindly afford us a copy of the written submissions filed by the Patentee in the said matter.

Yours faithfully,

  
Dhruva

Enc. A/a.

CC.: M/s. Depenning & Depenning, Advocates.

**BEFORE THE PATENT OFFICE AT CHENNAI**

In the matter of the Patents Act,  
1970

AND

In the matter of Indian Patent No.  
207232 granted to Indian Patent  
Application No. 959/MAS/1995 filed  
by F. Hoffmann-La Roche AG

AND

In the matter of post-grant opposition  
under section 25(2) of the Patents  
Act, 1970 by Delhi Network of  
Positive People

Delhi Network of Positive People                      )      Opponent

F. Hoffmann-La Roche AG                                      )      Patentee

**WRITTEN SUBMISSIONS ON BEHALF OF OPPONENT**

**I.      INTEREST OF THE OPPONENT**

1.      The Opponent is a network of persons living with HIV and is a legal entity comprising persons living with HIV (PLHIV). Amongst its other functions, it advocates for availability of affordable treatment for HIV related illnesses. When their immune systems

are compromised because of HIV, PLHIV are susceptible to cytomegalovirus (CMV), which can lead to CMV retinitis. If left untreated, this can even cause blindness in PLHIV. The Opponent is therefore concerned about valganciclovir, one of the drugs used to treat CMV. It is concerned that if a patent exists on valganciclovir, the Patentee will have a monopoly. A patent should be granted only if the patent application satisfies the criteria of patentability. It is submitted, for reasons set out below, that the criteria are not satisfied in the present case. The Patentee, which owns the patent on valganciclovir in India and other countries, charges as much as US\$ 10,000 for a four-month supply of oral valganciclovir. In India, the price for a full course of treatment at the price offered by the Patentee is over Rs. 270,000 (Rs.1040/tablet\*264), far out of reach for the vast majority of people in need of treatment. Failure to access this medicine could result in many PLHIV being doomed to life of blindness, in spite of it being a treatable condition. The Patentee, in its reply statement, has not denied the existence of the Opponent, its membership or its work. It is therefore not entitled to argue on these issues [See Reply Statement, at page 2, para (b)]

## II. STANDING OF OPPONENT

2. Section 2(1)(t) of the Patents Act defines a person interested as "person interested' **includes** a person engaged in, or in promoting, research in the same field as to which the invention relates" (emphasis supplied).

3. Thus, it is clear that the definition of “person interested” is an **inclusive definition**.
4. In *Ajay Industrial Corporation v. Shiro Kanao*, AIR 1983 Del 496, the Delhi High Court held that the expression “person interested” includes a person with public interest [See page 502, para 10]. Undisputedly, the Opponent is a person who has public interest on the issue of access to medicines, especially valganciclovir.
5. Internationally too, persons living with HIV and their organisations have been identified as a “person interested” in patent proceedings. Thus, in *AIDS Access Foundation and others v. Bristol-Myers Squibb and Another*, the Central Intellectual Property and International Trade Court of Thailand held that the expression “person interested” includes an organisation representing persons living with HIV.
6. Relying on the decision of the Patent Controller in a post-grant opposition by *Sankalp Rehabilitation Trust v. F. Hoffmann-La Roche AG*, the Patentee argued that the Opponent has no locus. However, the issue of whether or not the Opponent is a “person interested” was not disputed in the pleadings and therefore was not an issue in the matter. Therefore, the decision is of no relevance to the case at hand.
7. Thus, the Opponent who is an organisation comprising persons living with HIV is a “person interested” within the meaning of section 2(1)(t) of the Patents Act and therefore has locus to file the present post-grant opposition.

### III. PATENT OFFICE OUGHT TO STRICTLY INTERPRET PATENTABILITY STANDARDS.

8. In order to comply with its obligations under the *Trade Related Aspects of Intellectual Property Rights* ("TRIPS"), India extended patent protection to pharmaceutical products through the 2005 Patent Amendment. However, bearing in mind the implications of patents on the affordability and accessibility of medicines, the Doha WTO Ministerial Conference adopted the *Doha Declaration on the TRIPS Agreement and Public Health* (the "Doha Declaration") in 2001. Paragraph 4 of the Doha Declaration, in relevant part, states "we affirm that the [TRIPS] Agreement can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health **and, in particular, to promote access to medicines for all**". (emphasis added). The Doha Declaration is binding on all WTO member states.
9. It is against this background that Parliament amended the patent law in 2005 and introduced higher patentability standards as safeguards—such as the definition of inventive step in section 2(1)(ja) and amendment to section 3(d)—to attempt to prevent trivial patents [See para 9 of Statement of Opponent].
10. The objective of the Patent Amendment Act, 2005 has been emphasised by the Madras High Court, which held: "We have borne in mind the object which the Amending Act wanted to achieve namely, **to prevent evergreening; to provide easy access to the citizens of this country to life saving drugs and to discharge their**

***Constitutional obligation of providing good health care to its citizens.***" [See Novartis AG and Another v. Union of India and Others, (2007) 4 MLJ 1153, para 19, at **Exhibit A** to Statement of Opponent].

11. Similarly, the Patent Office at New Delhi has adopted the standard of strict scrutiny to patent applications on essential medicines [See para 11 of Statement of Opponent; and Decision, In the Matter of Patent Application No. 2485/DEL/1998, The Patent Office, New Delhi, 11 June 2008 at Exhibit B to Statement of Opponent].
12. The Hon'ble Intellectual Property Appellate Board (IPAB) too has accepted that India has strict standards of patentability [See Novartis AG v. Union of India and Others, IPAB, 26 June 2009, at page 157, para xix].
13. The Hon'ble Patent Office therefore, while examining patent applications and the validity of patents, must bear in mind the legislative object of ensuring TRIPS compliance while ensuring that patent protection does not come in the way of India's fundamental duty to provide good health care to its citizens. Therefore, the Hon'ble Patent Office ought to strictly interpret the patentability standards to prevent trivial patenting.

#### **IV. NO PRESUMPTION OF VALIDITY**

14. Under Indian law, there is no presumption of validity of a patent as is sought to be argued by the Patentee [See section 13(4) of Patents Act and Bishwanath Prasad Radhey Shyam v. Hindustan Metal Industries, MANU/SC/0255/1978, para 31].

15. It is also an established position of law that there is no presumption of validity of patents, especially in respect of recently granted patents [See *F. Hoffmann-La Roche Ltd. v. Cipla Limited*, MANU/DE/0517/2008, at para 62].
16. The Patentee seeks to rely on the amendment of the Form of grant of a patent to support its proposition that a patent is presumed to be valid. However, no Form made by the Central Government can take away from the substantive provisions of section 13(4) of the Patents Act.
17. Similarly, reliance by the Patentee on the decision of courts of the United States in support of the proposition of presumption of validity of patents is erroneous in view of the provisions of the Indian Patents Act.
18. Relying on *Re Procter & Gamble Company's Application*, [1982] RPC 473, the Patentee sought to argue that if a conflict of expert evidence creates a reasonable doubt whether an opponent's case is made, the patent should be granted and the opponent left to ventilate the objection in revocation proceedings. However, this decision is of no relevance at all in India or to the present case. That case arose in the context of summary pre-grant opposition proceedings, which were available under section 14 of the then Patents Act, 1949.

## **V. BACKGROUND**

19. The alleged invention in the present case is the L-valyl ester prodrug of an admittedly known molecule, ganciclovir

[valganciclovir], which allegedly exhibits improved absorption characteristics. [See Complete Specification, pages 2–7]

20. Pertinently, at least the following have been admitted by the Patentee as forming the state of the art: (1) that ganciclovir, its utility against virus of herpes family, and its shortcomings resulting from a lack of oral bioavailability were well known; (2) that the strategy of developing a suitable prodrug for ganciclovir was well known to overcome these known difficulties; (3) that acyclovir, a substance identical in chemical structure save the absence of single hydroxymethyl group, with similar utility, was well known; and (4) that the L-valyl ester of acyclovir was known to demonstrate improved oral bioavailability [See Statement of Opponent, paras 13 to 15].

#### **IV. GROUNDS**

21. The Opponent has raised the following amongst other grounds, which are without prejudice to one another.

##### ***A. Claims 1 to 9 and 12 lack novelty.***

22. The Opponent submits that claims 1-9 and 12 lack novelty, and therefore fail under the definition of "invention" in section 2(1)(j) of the Act. Therefore, under section 25(2)(b), given that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim...(ii) in India or

elsewhere, in any other document, the claims of the patent ought to be revoked.

23. The Opponent submits that claims 1 to 9 and 12 have been fully described in and are anticipated by the disclosures contained in United States Patent 5,043,339 to Beauchamp, granted on 27 August 1991 [hereinafter referred to as "the '339 patent"] [See Exhibit D to Statement of Opponent].

24. The '339 patent describes amino acid esters of ganciclovir. It specifically discloses the mono- and di-esters of the above compound, and the preferred amino acids are L-amino acids chosen from the group of "glycine, alanine, **valine**, and isoleucine" in order to improve its oral bioavailability [See '339 patent, column 2, lines 22-29 and Statement of Opponent, paras 20 to 23].

25. The '339 patent further discloses that the compounds may be prepared as physiologically acceptable salts and lists the hydrochloride and acetate salts as suitable candidates [See '339 patent, column 2, lines 32-36]. It also discloses that the compounds described therein may be presented as "pharmaceutical formulations" comprising the compounds "together with more or more acceptable carriers" [See '339 patent, column 3, lines 45-55]. In light of this, claims 1 and 5 to 8 and 9 lack novelty.

26. Importantly, the '339 patent also discloses that "the compounds according to the invention may be prepared in a **conventional manner**." [See '339 patent, column 5, lines 62-64].

27. It is an established position of law that an enabling disclosure is sufficient to anticipate a compound. [See *Synthon BV v. Smithkline*

*Beecham plc*, [2005] UKHL 59, at para 26, 27, 30, 32]. Enabling disclosure is one which allows the person skilled in the art to arrive at the compound with some amount of trial. There is thus no need for the prior art document to give specific examples.

28. Claims 1, 2, 5 and 6 claim either a mixture of (R)- and (S)- diastereomers of mono-L-valine ester of ganciclovir or each of them individually. However, given that the mono-L-valine ester of ganciclovir was disclosed in the '339 patent, as demonstrated above, each of its diastereomers were also *inherently disclosed* by the '339 patent to a person skilled in the art. Diastereomerism is an inherent feature of any given molecule that is strictly determined by its molecular structure. As such, the disclosure in the prior art of a molecule with one or more chiral centers will inherently disclose each of its possible diastereomers, both individually and in mixture. Therefore, claim limitations in Claims 1, 2, 5 and 6 relating to diastereomers are insufficient to confer novelty to these claims [See Statement of Opponent, paras 26 to 27].

29. Claim 4, which relates to crystalline form, is also anticipated on account of inherency of formation of crystalline form.

30. Thus, these disclosures are sufficient to destroy the novelty of each and all of claims 1-9 and 12.

31. This is supported by the expert affidavits of Dr. Nitya Anand and Dr. Leena Rao [See Expert Affidavit of Dr. Nitya Anand, paras 33 to 46 and Expert Affidavit of Dr. Leena Rao, paras 22 to 33].

32. Further, the affidavit of Dr. Valentino Stella on behalf of the Patentee does not deny that the '339 patent discloses the mono-esters of ganciclovir.
33. It is a matter of record that claims identical to claims 1 to 3 and 5 to 8 did not survive examination before the United States Patents and Trademark Office [See Exhibit F to Statement of Opponent].
34. The fact that the '339 patent discloses a slightly broader class of compounds (all with the same utility) is immaterial. The prior generic disclosure of a slightly larger class of compounds than what is being claimed can nonetheless be sufficient to anticipate the claimed compound.
35. At the hearing, the Patentee sought to argue that the present patent is a case of a valid selection patent and relied on several judgments including *Apotex v. Sanofi*, 2006 FCA 421 and *Pfizer Canada Inc v. Canada*, [2009] 1 F.C.R. 253 in support of its proposition. However, this argument is not available to the Patentee. Firstly, there is nothing in the pleadings (either the specification or the reply statement) to support this. Secondly, on the contrary, the Patentee denies that the '339 patent discloses or describes the compounds of Indian Patent No. 207232 [See Patentee's Reply Statement, paras 17 and 19]. Therefore, all judgments cited by the Patentee in support of selection patents are inapplicable to the case at hand.
36. Without prejudice to the above, the Opponent submits that the doctrine of selection patents is a common law doctrine, which is not applicable to India in light of the amendments to the Indian patent law.

Section 3(d) of the Patents Act statutorily overrides the common law doctrine of selection patents.

37. The Patentee relied on *Impax Laboratories Inc. v. Aventis Pharmaceuticals Inc.*, 468 F.3d 1366 (2006). This judgment does not support the Patentee. In fact, it holds that a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art. It further refers to *In Donohue*, 766 F.2d 531 (Fed. Cir. 1985) which expressly states that a claimed invention is placed in public possession "if one of ordinary skill in the art could have combined the publication's description with his own knowledge to make the claimed invention" [See Impax, at page 1381, i.e. page 9, column 2].

38. The Patentee also relied on *Apotex v. Sanofi*, 2006 FCA 421. As stated earlier, this is a case on selection patents and is not applicable to the present case in the absence of pleadings. Even otherwise, this does not support the Patentee as the ratio in that case, if applied to the present case, shows that if one follows the disclosures in the '339 patent, one will obtain the mono-L-valine ester of ganciclovir.

39. The Patentee further relied on *Pfizer Canada Inc v. Canada*, [2009] 1 F.C.R. 253. Again, this is a case on selection patents and is not applicable to the present case in the absence of pleadings. Even otherwise, this case involved a broad class of compounds, which is not the present case. The '339 patent specifically discloses ganciclovir and its mono- and di-esters [See '339 patent, column 2].

**B. Claims 1 to 12 lack inventive step.**

40. Without prejudice to the above, the Opponent submits that claims 1 to 12 lack inventive step. Therefore, under section 25(2)(e), given that the invention so far as claimed in any claim of the complete specification invention so is obvious and clearly does not involve any inventive step, having regard to what the matter published has been published before the priority date of the claim, the claims of the patent ought to be revoked.

41. As stated earlier, Parliament has sought to set higher patentability standards by defining "inventive step". Section 2(1)(ja) of the 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". Thus, the Patentee is required to show that the alleged invention involves a **technical advance** and is **not obvious** to a person skilled in the art. This is in order to ensure that patents are granted only to genuine inventions.

42. As stated earlier, the complete specification itself discloses:

- (i) Ganciclovir, its utility, and the problem of overcoming the low oral bioavailability of ganciclovir was well-known and described in the art prior to the Priority Date [See page 2]
- (ii) Strategy of developing a suitable ester prodrug for ganciclovir and other similar drugs in order to overcome these problems [See pages 3 to 7]
- (iii) Conversion of acyclovir – **a compound identical to ganciclovir save the absence of a single hydroxymethyl**

**group** – to an L-valine ester prodrug, which exhibited improved oral bioavailability.

43. Specifically, Beauchamp, et al., "Amino acid ester prodrugs of acyclovir," *Antiviral Chemistry & Chemotherapy*, 3(3) 157-164 (1992) (hereinafter referred to as "Beauchamp (1992)") tested and evaluated 18 amino acid esters of acyclovir. After testing the various amino acid esters of acyclovir, the authors concluded that, as between the D- and L-isomers of the various amino acid esters tested, there was a decided preference for the naturally occurring L-isomer. It also taught a preference for the hydrochloride salt of L-valyl ester prodrug of acyclovir [See Exhibit G to Statement of Opponent, at pages 161–162].
44. Beauchamp (1992) also specifically teaches the possible contribution of a stereospecific transporter and the advantages of the side chain of the L-valyl ester. i.e. optimal combination of chain length and branching at the beta-carbon [See Beauchamp (1992), at page 161].
45. Further, Beauchamp (1992) should be read as a whole. It is incorrect to pull out statements from their context and draw inferences as sought to be done by the Patentee.
46. Similarly, United States Patent 4,957,924 to Beauchamp, granted on 18 September 1990 (the '924 patent), discloses "Therapeutic Valine Esters of Acyclovir and Pharmaceutically Acceptable Salts Thereof" [See '924 patent at Exhibit H to Statement of Opponent]. It describes the L-valyl ester of acyclovir, its crystalline form [See column 8, lines 22-33], its pharmaceutically acceptable salts, and pharmaceutical compositions comprising the claimed compound. The '924 patent

disclosed that the L-valyl ester of acyclovir showed a 63% urinary recovery as acyclovir when tested on rats, and concluded that it "shows remarkably improved oral bioavailability compared with acyclovir and compared with previously disclosed amino acid esters of acyclovir" [See '924 patent, column 12, lines 52-68].

47. Therefore, in light of this, when faced with the problem of developing a form of ganciclovir with improved oral absorption characteristics, a person skilled in the art would have applied the abovementioned teachings of the successful discovery of an amino acid prodrug of acyclovir, as the compound is nearly identical with ganciclovir with similar utilities.
48. Therefore, claims 1-9 and 12, which merely claim some combination of the mono-L-valine ester of ganciclovir, its inherently existing diastereomers, its pharmaceutically acceptable salts, its inherent crystalline form, or its pharmaceutical compositions, all lack inventive step in light of the '339 patent, Beauchamp, et al and the '924 patent—individually and in combination.
49. Further, process claims 10 and 11, which merely describe the process by which the mono-L-valine ester of ganciclovir and its pharmaceutically acceptable salts are obtained, are obvious in light of the '339 patent, to the extent that they describe conventional means that are well known in the art. Therefore, they lack inventive step.
50. ***Pertinently, the complete specification states that the alleged problem sought to be solved was that of improving bioavailability. Though it refers to Beauchamp (1992), there is no mention whatsoever of the expected problem of toxicity due to***

***phosphorylation of the free hydroxyl group, if this was applied as a solution.***

51. The Patentee, relying on another article authored by Beauchamp (1993), argued that Beauchamp (1992) teaches away from the present invention for reasons of expected toxicity due to phosphorylation of the free hydroxyl group in mono-L-valine ester of ganciclovir [*See for example, Reply statement of Patentee, para 36*]. It also relied on expert affidavits filed on its behalf to support this proposition. However, it is clear from a reading of Beauchamp (1992) that the aim of Beauchamp (1992) was not to examine the issue of toxicity, but the development of a molecule with improved bioavailability. Further, even Beauchamp (1993) merely accords priority to molecules without free hydroxyl groups but does not rule out the possibility of developing ester prodrugs with a free hydroxyl group, such as in the present case [*See expert affidavit of Dr. Nitya Anand, paras 51 to 68*]. Therefore, without prejudice to the argument of anticipation, a person skilled in the art who is aware of the disclosures of the '339 patent, Beauchamp (1992) and Beauchamp (1993) would examine both the mono- and di-L-valine ester prodrugs of ganciclovir to seek a solution to the problem of oral bioavailability and not rule out the mono-L-valine ester prodrug.
52. The decision of *Apotex v. Sanofi*, 2006 FCA 421, relied on by the Patentee, was given in the background of the impossibility of predicting the claimed advantages [*See para 43, page 19*]. That is not the case here in view of the expected advantages of bioavailability of

L-valyl ester prodrugs as reported in the '339 patent and other prior art documents with respect to acyclovir.

53. The Patentee relied on *Eisai Co. Ltd. v. Dr. Reddy's Laboratories Ltd.*, CAFC. However, this does not support the Patentee. That case involved the identification of the lead compound, which was to be the anchor for the obviousness argument. In the present case, however, the lead compound is already identified and not in dispute. Further, the disclosures by Beauchamp (1992) and the '924 patent provided enough reason to consider the mono-ester of ganciclovir.

54. The Patentee further relied on *Procter & Gamble v. Teva*, CAFC, to point out the secondary considerations of obviousness. However, the Indian patent law statutorily defines inventive step in section 2(1)(ja) and excludes the test of secondary considerations to determine non-obviousness, which has been developed by US courts. The Patentee has to meet the standard of inventive step set out in the Indian law. Without prejudice to the contention above, *Procter & Gamble* recognises that structural similarity of compounds is generally deemed to create a *prima facie* case of obviousness [See *ibid*, page 7]. Secondly, it holds that to argue that a new compound is obvious, the challenger may show that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention [See *ibid*, pages 7-8]. In the present case, acyclovir and ganciclovir admittedly have structural similarities.

55. Similarly, the Patentee relied on *In re Baird*, 16 F.3d 380 (Fed Cir. 1994), and cites the part relating to the doctrine of suggestion. However, again, the teaching-suggestion-motivation test was

developed by the US federal courts. Further, the relevance of this judgment is doubtful after the decision of the United States Supreme Court in *KSR v. Teleflex*, where the Court overturned a decision of the Federal Circuit Court which applied the teaching-suggestion-motivation method.

**C. Claims 1 to 9 and 12 fail under section 3(d).**

56. The Opponent submits that claims 1 to 9 and 12 are new forms of known substances, which do not exhibit enhanced therapeutic efficacy as required under law. Therefore, claims 1 to 9 and 12 fail under section 3(d).
57. Section 3(d) allows patenting of new forms of known substances, only if the new form exhibits significant efficacy over the efficacy of the known substance.
58. The Hon'ble Madras High Court, in *Novartis AG v. Union of India and others*, (2007) 4 MLJ 1153, has held that section 3(d) requires a showing of increased **therapeutic efficacy** [See pages 18 to 20, para 13 of Exhibit A to Statement of Opponent.]. The interpretation of the expression efficacy by the Hon'ble Madras High Court is not *obiter dicta*, as the Patentee seeks to argue. The Hon'ble Madras High Court was examining the issue of constitutional validity of section 3(d) in light of Novartis' allegation that the term "efficacy" is vague and has no meaning, and therefore **the interpretation by the Hon'ble Madras High Court is not obiter and is binding on the Patent Office.**

59. The Patentee relied on *Amar Nath Om Prakash v. State of Punjab and Others*, AIR 1985 SC 218 to argue that the expression “efficacy” elaborated by the Hon’ble Madras High Court should not be construed as a statute. However, as stated above, the Hon’ble Madras High Court was required to interpret the meaning of efficacy, and it interpreted it as therapeutic efficacy. This has been independently interpreted by the IPAB—a specialist body—in the *Novartis* case to mean therapeutic efficacy, which excludes bioavailability. That does not amount to construing the judgment of the Hon’ble Madras High Court like a statute.
60. The Patentee also relied on decision of the Delhi Patent Office in respect of Patent Application No. 396/DEL/1996. However, this does not support the Patentee. The Controller, in that case, observed that the Hon’ble Madras High Court has defined efficacy in respect of pharmacological compounds. Secondly, though the Controller declined to hold the decision of the Patent Controller in the *Novartis* case as conclusive because of the pending appeal, that is no longer the case now. The IPAB has now decided the appeal in the *Novartis* case and interpreted the term “efficacy” as therapeutic efficacy in relation to pharmaceuticals.
61. The burden of proving this enhanced efficacy is on the patent applicant / patentee. The Hon’ble Madras High Court, in *Novartis AG v. Union of India and others*, (2007) 4 MLJ 1153, has held that the burden of proof is on the patent applicant to show an increase in therapeutic efficacy [See pages 18 to 20, para 13 of Exhibit A to Statement of Opponent].

62. The Patentee argued that the decision of the Hon'ble Madras High Court relates only to a pre-grant opposition proceeding and not to post-grant opposition proceedings. However, this is not correct. Firstly, the Hon'ble Madras High Court was generally deciding the question of constitutional validity of section 3(d), which serves as a ground of opposition in pre- and post-grant opposition proceedings as well as revocation proceedings. The appeals against the Patent Controller's decision in the pre-grant oppositions against the patent application relating to Gleevec were an independent set of cases and these proceedings were not referred to or decided by the decision of the Hon'ble Madras High Court referred to above. Therefore, **the decision of the Hon'ble Madras High Court with respect to the issue of burden of proof on the patent applicant is binding in all patent proceedings.** Secondly, **it is an established position of law that the burden of proving a fact within a person's knowledge is on that person** [See section 106 of the Evidence Act].

63. Assuming without admitting that '339 does not disclose the mono-L-valine ester, the known substance is ganciclovir and its various known esters which are considered to be the same substance under the explanation. Therefore the Patentee has to show that the mono-L-valine ester of ganciclovir and each of its claimed limitations is significantly more therapeutically efficacious as compared to ganciclovir.

64. The complete specification does not contain any data with respect to increased therapeutic efficacy.

65. The Patentee seeks to argue that increased bioavailability indicates increased efficacy of its alleged invention. To support this, the Patentee has provided data to show an alleged increase in bioavailability of the acetate and hydrochloride salts of the mono-L-valine ester over ganciclovir and its bis-esters [See Complete Specification, page 54].

66. However, this does not satisfy the requirement of section 3(d).

67. Firstly, bioavailability is different from efficacy [See Novartis AG v. Union of India and Others, IPAB, 26 June 2009, at pages 155–156, para xviii]. Further, other advantageous properties such as better shelf life, better storability and better flow properties are related to formulation or presentability of a substance and have no relationship with efficacy [See Novartis AG v. Union of India and Others, IPAB, 26 June 2009, at pages 157–158, para xxi]. This is supported by the understanding of the term efficacy in the pharmaceutical field. Efficacy is understood to mean the relative intensity with which the agonists vary in response they produce when they occupy the same number of receptors and with the same affinity. [See Exhibit I to Statement of Opponent, at page 161]. It is that property intrinsic to a particular drug that determines how “good” an agonist the drug is [See relevant extracts from Goodman and Gilman (11<sup>th</sup> edition), at internal page 35]. In other words, **it is the response that the drug is able to produce at the target site. It is an admitted position that the claimed invention converts into ganciclovir when ingested. Therefore there can be no question of increased efficacy.**

68. Secondly, assuming without admitting that increased bioavailability can indicate increased therapeutic efficacy, **the complete specification does not provide data of increased bioavailability of the mono-L-valine ester of ganciclovir, its R- and S-diastereomers, the crystalline form and other claim limitations. In fact, as far as the crystalline form is concerned, the complete specification admits that the only advantage is the ease of production** [See Complete Specification, at page 40, lines 20 to 23], which is not therapeutic efficacy.
69. *Ex facie*, the complete specification does not disclose any increase in efficacy as required under law. Therefore, claims 1 to 9 and 12 fail under section 3(d) read with section 25(2)(f) of the Patents Act.

***D. Claim 9 fails under section 3(e).***

70. Claim 9 relates to a composition of the mono-L-valine ester prodrug of ganciclovir with an acceptable carrier material or an excipient.
71. An excipient or a carrier is not pharmaceutically active and have any therapeutic properties. Therefore there cannot be any synergistic effect.
72. Further, the complete specification does not claim any synergistic effect.
73. Therefore, claim 9 relates to a mere admixture without any synergistic effects, and therefore fails under section 3(e) read with section 25(2)(f) of the Patents Act.

## **V. EXPERT AFFIDAVITS**

74. The expert affidavits of Dr. Valentino Stella and Dr. Mitscher do not disclose their interest.

75. *Ex facie*, it is clear that the experts have not deposed entirely on personal knowledge with respect to the contents of their affidavits.

76. Further, the experts merely refer to some documents and do not annex them. Further, while some documents are annexed, they are not proved in a manner known to law.

77. Specifically, with respect to the affidavit of Dr. Valentino Stella, the following need to be noted:

- (i) The affidavit does not disclose any interest the deponent might have in relation to the Patentee.
- (ii) The affidavit does not disclose whether Dr. Stella has worked on antivirals.
- (iii) With respect to the '339 patent, it does not deal with the disclosure of the L-valyl ester [See Dr. Stella's affidavit, paras 62-63].
- (iv) Paras 67 and 68 of Dr. Stella's affidavit have to be read as a whole. The affidavit does not take into account that the main problem dealt with by Beauchamp (1992) was poor oral bioavailability and does not deal with the fact that it indicated the particular advantages of the L-valyl ester prodrug. [See also expert affidavit of Dr. Nitya Anand, paras 51 to 68].
- (v) A careful reading of paras 81 to 82 shows that Dr. Stella states: "The Beauchamp '339 patent does not teach or

suggest mono-L-valine esters of ganciclovir with 3-hydroxy groups as hydrochloride salts." It clearly does not deny that the '339 patent discloses the mono-L-valine ester of ganciclovir or its other salts. In any event, the Opponent submits that the '339 patent discloses even the hydrochloride salts of the mono-L-valine ester of ganciclovir.

- (vi) Paras 84 to 91 of Dr. Stella's affidavit deal with the so-called secondary considerations of non-obviousness. However, the test of secondary considerations is not applicable in Indian law, which has a higher standard of inventive step.
- (vii) Para 91 of Dr. Stella's affidavit deals with an alleged increase in bioavailability. Firstly, as stated above, bioavailability is not the same as efficacy as held by the Hon'ble IPAB. Secondly, without prejudice to the above, Dr. Stella refers to certain data on animal work without disclosing the source of this information, viz. whether it is personal or based on private information made available to him. Therefore, this cannot be relied upon.
- (viii) Dr. Stella's affidavit does not discuss the '924 patent relating to acyclovir, which has been cited by the Opponent.

78. Specifically, with respect to the affidavit of Dr. Lester A Mitscher, the following need to be noted:

- (i) The affidavit does not disclose any interest the deponent might have in relation to the Patentee.
- (ii) The details set out in the CV not supported by documents. Except for statement, there is nothing.

- (iii) The affidavit does not disclose whether Dr. Mitscher has worked on antivirals.
- (iv) In para 32, Dr. Mitscher makes statements about medicine, which do not pertain to medicinal chemistry—his alleged field of expertise.
- (v) In para 68, Dr. Mitscher states that Beauchamp teaches away from claimed invention. However, it does not address the fact that the papers address the problem of poor bioavailability and the advantages of the L-valyl ester as disclosed by Beauchamp [*See also expert affidavit of Dr. Nitya Anand, paras 51 to 68*].
- (vi) Para 72 of Dr. Mitscher's affidavit ignores the teaching to prepare the L-valyl ester prodrug of acyclovir and that it sets out specific general principles for development of prodrug, which includes considering chemical derivatives that do not block phosphorylation sites.
- (vii) Para 76 of Dr. Mitscher's affidavit does not deny that the '339 patent discloses the mono-L-valine ester of ganciclovir and its other salts.
- (viii) In para 77 of his affidavit, Dr. Mitscher ignore the discussion on pages 161 and 162 of Beauchamp (1992) paper.
- (ix) Paras 97 and 98 of Dr. Mitscher's affidavit are not supported by data to prove the alleged increased bioavailability of the mono-L-valine ester. Pertinently, in para 97, Dr. Mitscher only claims an enhanced transport for the mono-L-valinate ester of ganciclovir, which he does not deny is already disclosed by the

'339 patent. Further, clinical efficacy is different from therapeutic efficacy.

- (x) Dr. Mitscher's affidavit does not discuss the '924 patent relating to acyclovir, which has been cited by the Opponent.

79. Specifically, with respect to the affidavit of Dr. Per L\_Jungman, the following, amongst other issues, need to be noted:

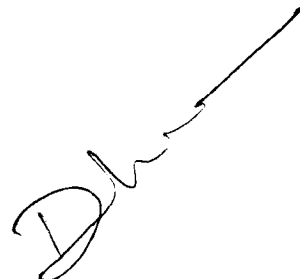
- (i) The affidavit of Dr. Jungman discloses that he is not a biochemist or pharmacologist.
- (ii) In para 40, Dr. Jungman states that valganciclovir has a bioavailability of approximately 10 times that of oral ganciclovir. However, there is no reference to the source of the data.
- (iii) In para 42, Dr. Jungman refers to other studies for data on valganciclovir. However, it does not appear to be of his own personal knowledge, but a reliance on other studies which are not proved.

## VI. CONCLUSION

80. In light of the Notice of Opposition, Statement of Opponent and all pleadings and evidence filed by the Opponent, the Opponent submits that any patent granted to Patent Application No. 959/MAS/1995 ought to be revoked.

Place: Chennai

Date: 24 September 2009

A handwritten signature in black ink, appearing to be 'Dr.' followed by a stylized name, with a long horizontal line extending from the end.