THE PATENTS ACT, 1970

(39 of 1970)

as amended by

THE PATENTS (AMENDMENT) ACT, 2005

(15 of 2005)

(with effect from 1-1-2005)

&

THE PATENTS RULES, 2003

as amended by

THE PATENTS (AMENDMENT) RULES, 2006

(with effect from 5-5-2006)

M/s F.HOFFMANN-LA ROCHE AG
a Swiss Company of 124 Grenzacherstrasse,
CH-4002,
Basel, Switzerland.
Represented by
Mr. Pravin Anand of Anand & Anand,
Mr. D.J.Solomon of De Penning & De Penning

..... Patentee

1. M/s Ranbaxy Laboratories Ltd.,
   A-11,Sahibzada Ajit Singh
   Nagar,Ropar District, Punjab, 160 055
   Represented by Mr. R.Parthasarathy
   of Lakshmikumaran and Sridharan

2. M/s Cipla Ltd., 289, Bellalis Road,
   Mumbai Central, Mumbai – 400 008
   Represented by Mr. S.Majumdar,
   Dr. Sanchita Ganguli of S.Majumdar &
   Co.,
   Mr. A.Ramesh Kumar

3. M/s Bakul Pharma Pvt. Ltd., of Sterling Centre, 4th Floor, Dr. A.B. Road, Worli, Mumbai – 400 018

   Represented by Mr. S.Majumdar,

   Dr. Sanchita Ganguli of S.Majumdar & Co.,

4. M/s Matrix Laboratories Limited, 1-1-151/1, IV Floor, Sairam Towers, Alexander Road, Secunderabad – 500 003

   Represented by Mr. K. Feroz Ali

5. Delhi Network of Positive People, Galli No. 3, House No. 64, Village Neb Sarai, New Delhi – 110 068

   Represented by Mr. Anand Grover

6. Indian Network for People living with HIV/AIDS & The Tamil Nadu Networking People with HIV/AIDS, New No. 41 (old No 42/3), Second Main Road, Kalaimagal Nagar, Ekkaduthangal, Chennai – 600 097. (Rejoinder)

   Represented by Mr. Anand Grover

..... Opponents

Dr. Bindu Jacob Examiner of Patents & Designs

1. History of the proceedings

1. M/s F.HOFFMANN-LA ROCHE AG a Swiss Company of 124 Grenzacherstrasse, CH-4002, Basel, Switzerland, hereinafter referred as 'patentee', have filed an application for patent for their invention titled '2-(2-AMINO-1,6-DIHYDRO-6-OXO-PURIN-9-YL)METHOXY-1,3-PROPANEDIOL DERIVATIVE' on 27th day of July 1995 through their agent M/s De Penning and De Penning and it was numbered as 959/MAS/1995 having priority of United States of America (US).

2. The agent filed a request for examination of application for patent on 27th July 2004 and the application was published under section 11(A) of the Patents (Amendment) Act, 2005, herein after referred as 'Act' in the Patent Journal No. 06/2005 dated 25th February 2005.

3. The application was taken up for the examination and the First Examination Report (FER) was issued on 17th May 2006.

4. The patent was granted with patent number 207232 and published on 29.06.2007 in the Journal of the Patent Office. M/s Ranbaxy Laboratories Ltd., M/s Cipla Ltd., M/s Bakul Pharma Pvt. Ltd., M/s Matrix Laboratories Limited, Delhi Network of Positive People and Indian Network for People living with HIV/AIDS & The Tamil Nadu Networking People with HIV/AIDS (Rejoinder) hereinafter referred as 'opponents' have filed a post-grant opposition through their attorneys under section 25 (2) of the Act within the time limit.

2. Grounds of opposition

5. The Grounds of opposition filed under section 25(2) (b), 25(2) (d), 25(2) (e), 25(2) (f), 25(2) (g), 25(2) (h) and 25(2) (i).

6. Documents submitted in the opposition

(i). EP0375329
(ii). US 5043339
(iii). US6083953
(iv). Prosecution history of US6083953 in the USPTO
(v). US 4355032
(vi). US 4957924
(vii). EP0187297
(viii). EP 0141927
(ix). US 5840891
(x). US 5856481
(xi). Gazette Notification dt 3rd Jan 1995

(xii). EP099493

(xiii). EP167385

(xiv). GB2104070

(xv). Beauchamp et.al, Antiviral chemistry and Chemotherapy (1992), 3(3), 157-164.

(xvi). Beauchamp et.al, Drugs of the Future, 1993, 18(7): 619-628

(xvii). J.Pharm.Sci.,vol.76.No.2,Feb 1987

(xviii). Martin et al.; Journal of Pharmaceutical Sciences 1987 76:180-184

(xix). British journal of Pharmacology(2006), 147, 1-11

(xx). J.Med.Chem., 26, 602 – 604

3. Subject matter of the invention

7. The specification describes the invention relates to mono L-valine ester of ganciclovir and its pharmaceutically acceptable salt. The object of the invention was to provide a compound with improved bioavailability when administered orally, set out by a formula I with a number of variables. The specification further describes the advantages of L-valine ester of ganciclovir and its pharmaceutically acceptable salt and compared with many other related compounds.

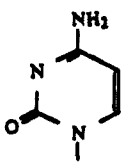
4. Novelty

8. The counsel for the opponents argued that the invention is not novel in view of US '339 which discloses various esters of ganciclovir at column 1, line 39

    i. "According to one feature of the present invention there is provided a formula I:

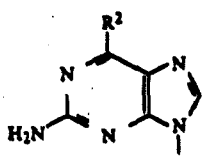
(I)

ii. wherein R and R^1 are independently selected from a hydrogen atom and a naturally occurring neutral amino acid acyl residue providing at least one of R and R^1 represents an amino acid acyl residue and B represents a group of formula



(A)

or



(B)

iii. in which R^2 represents a C_{1-6} straight chain, C_{3-6} branched chain or C_{3-6} cyclic alkoxy group, or a hydroxyl or amino group or a hydrogen atom and the physiologically acceptable salts thereof.

And column 2, line 17

'The amino acid acyl residue of the above compounds according to the invention may be derived for example from naturally occurring amino acids, preferably neutral amino acids i.e. amino acids with one amino group and one carboxyl group. Examples of preferred amino acids include aliphatic acids, e.g., containing up to 6 carbon atoms such as glycine, alanine, valine and isoleucine. The amino acid esters

according to the invention include the mono- and di-esters of the compound of formula (I). The amino acids may be D-, L- and DL-amino acids, with the L-amino acids being most preferred.'

'The above-mentioned physiologically acceptable salts are preferably acid addition salts derived from an appropriate acid, e.g., hydrochloric, sulphuric, phosphoric, maleic, fumaric, citric, tartaric, and lactic or acetic acid.'

According to the compound of Claim 1 of '339, B is hydroxyl and the preferred amino acid valine ester is mono form, R is H and R^1 is L-valine, the compound accomplished is valganciclovir and the preferred salt is hydrochloride salt. Therefore, the 339 document clearly discloses the L-valinate ester of ganciclovir hydrochloride.

9. Further EP '329 patent discloses the amino acid esters which includes the mono- and di-esters, the (R)- and (S)- form, list of amino acids for making said mono- and di-esters and salt making acids. Example 5 of EP'329 teaches a bis-(L-valinate) ester of ganciclovir and example 6(b) teaches the process to get mono-(L-alaninate) ester of ganciclovir along with bis-(L-alaninate) ester of ganciclovir in the ratio of 1:9. It is very clear from example 6(b) that the monoester was prepared and isolated. The counsel referred the patentee's submission that in all examples of EP'329 a threefold excess of the activated amino acid was used. A skilled person reading the above processes and aiming to make mono-ester compounds would readily appreciate that by reducing the amount of the amino acid added to the reaction to less than one stoicheometric amount, relative to the diol moiety (ganciclovir, in this case) the formation of substantial amount of mono-esterified compounds will occur.

10. Further the counsel stated that a Supplementary Protection Certificate has been granted to the applicant (Glaxo) for the EP '329 patent claiming valganciclovir hydrochloride for the UK authorized medicinal use

(treatment of cytomegalovirus retinitis in AIDS patients) which includes formulation, synthetic methods are covered by at least claims 1, 2, 5, 6, 7, and 9 to 14 and possibly claim 8 of the EP '329. It is very clear that valganciclovir is disclosed and enabled by EP'329 and the Patentee (Roche) was also aware of the fact that SPC which anticipates the invention as claimed in patent 207232.

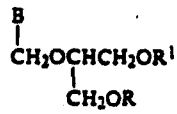
11. The corresponding US Patent 6,083,953 to Indian Patent 207232 was granted for crystalline form of valganciclovir hydrochloride and not for valganciclovir in its (R) - or (S) - form. During prosecution all the claims relating to product, process and composition were rejected referring US'339 patent by the USPTO. Several identical claims with respect to the corresponding patent applications filed in the United States, including US Patent Application No.08/812991 and 10/603503 were rejected by USPTO in light of disclosures contained in the '339 patent. Therefore, claims of the claimed invention lack novelty.

12. Claims 1-9 and 12 lacks novelty in light of disclosures contained in US '339 and equivalent EP '329. '339 Patent discloses HCl and acetate salts of mono- and di- valine esters of ganciclovir with improved oral bioavailability. Also R- & S- diastereomers of L-monovaline ester of ganciclovir inherently disclosed in '339 patent.

13. US Patent '339 and EP '329 discloses mono and divalyl esters of ganciclovir and pharmaceutically acceptable salt which exhibits enhanced oral bioavailability. Therefore, Claim 1 and the dependent claims are not novel.

14. The counsel for the patentee argued that every opponent has relied upon US '339 or EP '329 to support the ground of anticipation, it is important to note that A2 publication of EP 0375329 was published on 27 June 1990 and B1 publication of EP 0375329 was published on 31 May 1995. Accordingly, only EP 0375329A2 (herein after referred to EP'329) is a valid prior art and

not EP 0375329B1, since the disclosure of US' 339 and EP'329 are identical, they are used interchangeably in this argument. US '339 patent discloses a compound of Formula (I)



wherein B is a cytosine or certain purine residues, and R and R1 are independently selected from a hydrogen atom and an amino acid acyl residue providing at least one of R and R1 represents an amino acid acyl residue. It also describes in broad generic terms a genus of thousands of compounds, but it contains no specific description of the mono L-valine ester of ganciclovir nor does it include any teaching that would motivate, direct or enable a person of ordinary skills in the art to make the said compound. According to US '339 col 2, lines 17 to 31. The amino acid acyl residue may be derived for example from naturally occurring amino acids, preferably neutral amino acids. Examples of preferred amino acids include aliphatic acids, e.g. ., containing up to 6 carbon atoms such as glycine, alanine, valine and isoleucine. The amino acid esters include mono and di-esters of the compound of formula 1. Accordingly, even the preferred embodiments of US '339 will encompass well over 400 compounds.

15. There are six examples in the US '339 patent demonstrating the preparation of preferred compounds of Formula (I). The examples employ an excess of esterifying agent which would not result in the production of mono-esters.

16. Example 1 is for the preparation of the bis-(L-isoleucinate) ester of the cytosine-derived nucleotide as the bis-acetate salt. Example 2 is for the preparation of the bis-(L-valinate) ester of the cytosine-derived nucleoside as the bis-acetate salt. Example 3 is for the preparation of the bis-(L-isoleucinate) ester of ganciclovir as the bis-acetate salt. Example 4 is for the preparation of the bis-(glycinate) ester of ganciclovir as the bis-acetate salt. Example 5 is for the preparation of the bis-(L-valinate) ester of

ganciclovir as the bis-acetate salt and Example 6 is for the bis-(L-alaninate) ester of ganciclovir as the bis-acetate salt. While the reference US' 339 mentions in Col. 2 Line 26 that the amino acid esters can include mono- and di-esters of the compound of formula (I), the US' 339 patent did not disclose mono-esters leave alone mono-(L)-valine ester of ganciclovir.

17. The genus of compounds disclosed in the US '339 patent is too broad and there is no landmark in the said US patent suggesting or disclosing the mono-(L)-valine ester of ganciclovir or any other monoester of ganciclovir. The said US patent does not even make any reference and teach that mono-ester of ganciclovir is a useful or desirable compound. Infact, the inventors of the US '339 patent teach that a free hydroxyl group in the prodrug is undesirable. The examples provided teach only the diesters and the monoester would not be expected to be formed using the procedures/process disclosed in the US' 339 patent which all utilize three-fold excess of the activated amino acid.

18. Further the counsel argued that the IPAB held in Gleevec order that working example is required in the prior art in order to establish the ground of anticipation.

> "We have carefully studied forming acids. The said compounds of formula I and salts there of are stated to be prepared in accordance with processes known per se. However, 1993 patent has not given any working example as to how a salt of imatinib could he made including imatinib mesylate", (pages 167 & 168 of IPAB order).

19. European Patent No.375329 discloses ester prodrug of ganciclovir and physiologically acceptable salts thereof having advantageous bioavailability when administered by an oral route. The patent however, does not disclose the utility as well as process for the preparation of mono esters of ganciclovir. Therefore it is an established position of law that an anticipating prior art document should name the claimed compound individually and should contain sufficient description, which should enable a person of

ordinary skilled in the art to arrive at the claimed invention without any further experimentation. Therefore, neither US'339 nor EP'329 disclose or contain "enabling disclosure" to carry out the claimed invention so as to render the US '339 as anticipating the claimed invention.

20. Also in **Synthon BV Vs. Smithkline Beecham Plc [2005] UKHL 59**, the courts held

> "30. Nevertheless, in deciding whether there has been anticipation, there is a serious risk of confusion if the two requirements are not kept distinct. For example, I have explained that for the purpose of disclosure, the prior art must disclose an invention which, if performed, would necessarily infringe the patent. It is not enough to say that, given the prior art, the person skilled in the art would without undue burden he able to come up with an invention which infringed the patent. But once the very subject-matter of the invention has been disclosed by the prior art and the question is whether it was enabled, the person skilled in the art is assumed to be willing to make trial and error experiments to get it to work. If therefore, one asks whether some degree of experimentation is to be assumed, it is very important to know whether one is talking about disclosure or about enablement"

21. Further to the Ranbaxy counsel's argument the counsel for the patentee contented that the Supplemental Protection Certificate (SPC) issued to Glaxo for EP patent '329B based on Roche clinical trails of Valganciclovir amounts to anticipation is totally false and baseless and is based on an incorrect understanding of SPC's vis-a-vis patents. Grant of patent and grant of SPC are two distinct issues. As EP 329 protects/ covers but does not specifically disclose valganciclovir, it is incorrect to state that the grant of SPC anticipates the IN '232 patent.

22. Further argued, IPAB had held that the documents related to the application to U.S. drug authority and U.S. term extension certificate and the test report of IIT and IICT were not knowledge available before the priority

date i.e.18.07.1997 of the instant application. We, therefore, cannot accept these as prior publications for consideration and cannot agree with R4 that these documents anticipate the appellant's subject compound. (page 168 of IPAB order).

23. In view of the above arguments, US '339 or EP '329 does not specifically disclose the mono-(L)-valinate ester of ganciclovir either expressly or inherently.

24. I am in an opinion that US'339 and the corresponding EP'329 do not explicitly disclose the compound of the claimed invention. The documents do not ascertain that the patents describe clear and unambiguous directions to make the compound of the claimed invention. Although the '339 and '329 patent generally discloses the existence of mono esters as part of a large class of compounds, it does not particularly disclose the compound or other property of the said compound. The information provided may be relevant but not appropriate to obtain the compound of the claimed invention. The prior art teachings would have been understood by the skilled person the date on which it was disclosed but not with the later invention. **The Technical Board of Appeal held in T/396/89 Union Carbide [1992] EPOR 312 at para 4.4**:

> "It may be easy, given a knowledge of a later invention, to select from the general teachings of a prior art document certain conditions, and apply them to an example in that document, so as to produce an end result having all the features of the later claim. However, success in so doing does not prove that the result was inevitable. All that it demonstrates is that, given knowledge of the later invention, the earlier teaching is capable of being adapted to give the same result. Such an adaptation cannot be used to attack the novelty of a later patent."

25. The examples provided in the said US'339 and EP'329 are related to diesters of ganciclovir, but not provided any hint to make the monoester.

Even though monoester is obtained as mono-(L-alaninate) ester of ganciclovir along with bis-(L-alaninate) ester of ganciclovir, it does not anticipate the mono-valinate ester of ganciclovir. The preferred compound in both the prior art documents are bis esters of amino acids such as glycine, alanine, valine and isoleucine. There was no teaching or direction in the prior art documents for making monoester of the present invention.

26. The filing date for obtaining the SPC is 27.8.2002 which is a subsequent information/knowledge that cannot be considered as a basis for determining anticipation of the present case.

5. Inventive step

27. The counsels for the opponents argued that US '924 disclose valine esters of acyclovir and pharmaceutically acceptable salts that exhibits more bioavailability than acyclovir. Acyclovir poorly absorbed when orally administered and large doses are needed to increase the oral bioavailability. Drugs having poor absorption are converted into ester to make the drug more bioavailable when administered orally. The amino acids ester of ganciclovir disclosed in EP '329 which includes mono- and di-esters, preferably D- L- and DL amino acids, more preferrably L-amino acids. It also teaches bis-(L-valinate) ester of ganciclovir and example 6(b) teaches the process to get mono-(L-alaninate) ester along with bis-(L-alaninate) ester of ganciclovir in the ratio of 1:9.

28. US '032 discloses ganciclovir and pharmaceutically acceptable salts thereof, which is highly active antiviral compound, particularly against Herpes Simplex Virus I and II and related viruses such as cytomegalovirus, Epstein-Barr virus and Varicella Zoster virus.

29. The oral form of parent drug ganciclovir has been commercially known from the US Patent '032. The L-valine ester of acyclovir has improved bioavailability than the acyclovir after oral administration. Ester forming amino acids, salt of the said esters, function of the ester salts and disease

targeted are known for the structurally similar acyclovir and ganciclovir. Therefore, person skilled in the art follows the route of L-valine ester of acyclovir i.e., Valacyclovir and apply same to ganciclovir to get valganciclovir. Valacyclovir and valganciclovir are nucleoside analogs having similar structure and used for the similar treatment.

30. Publications of Beauchamp in 1992 and 1993 disclosed the best amino-acid ester for acyclovir. There were 18 amino acid esters synthesized and tested as potential prodrugs, among those amino acid esters L-amino acid esters were better prodrugs than the corresponding D- or DL-isomers, particularly L-valyl ester was the best prodrug. Valacyclovir, the prodrug of acyclovir is more bioavailable than acyclovir that is proved to be rapid hydrolysis in vivo than the parent compound. Properties like aqua solubility, stability, antiviral activity and toxicological testing of the valine for making ester proved to be the choice of drug. Beauchamp have published many research publications in the field of antivirals, also inventor of valacyclovir and bisester form of ganciclovir. In the article Drugs Fut., 1993,18(7) page 627 said,

> 'Over many years of scientific exploration, the various attempts to develop an oral prodrug of acyclovir have revealed certain basic principles that should be applicable to other nucleoside analogs.'

31. Various forms of esters are prepared using hydroxyl group of the purine ring and side chain of acyclovir with amino acids. The modifications made to the purine ring was toxic and the modifications made to the acyclic chain resulted in improved effect.

32. Acyclovir and ganciclovir are structurally similar and functionally similar nucleoside analog. So it is obvious to a person would try for the similar ester which is already proved with improved effect. US '924 patent discloses the L-valinate ester of acyclovir and hydrochloride salt of the L-valinate ester. The diseases targeted by the two drugs L-valinate ester of acyclovir and ganciclovir are similar. L-valine is a chiral compound, its

derivative L-valinate ester of ganciclovir inherently will be a chiral molecule, therefore (R) or (S) diastereoisomers can be expected by a skilled artisan.

33. US '339 disclosed mono and di-esters of ganciclovir wherein ester forming group is selected from amino acids including glycine, alanine, valine and isoleucine, preferred amino acids are L-amino acids among D, L and DL – amino acids.

34. Using L- valine to prepare an ester with purine drugs is known in the art. Ganciclovir is structurally similar to acyclovir and both are anti-viral drugs. Valacyclovir was developed as a successful prodrug of acyclovir and its hydrochloride salt was marketed as a successful medicine. Beauchamp et. al disclosed L-valyl esters of acyclovir were the best prodrug of the esters investigated. A person skilled in the art would combine the teachings of Beauchamp's publications, US '032, US '339, EP '329 and US '924 to prepare the compound of the alleged invention viz., the L-valine ester of ganciclovir. Thus, it would have been obvious to a person skilled in the art of medicinal chemistry to prepare the hydrochloride salt of L-valine esters of ganciclovir with a more than reasonable expectation of success with the teachings of the said prior art.

35. The counsel for the patentee contented that none of the documents US'339, EP'329, Beauchamp, 1992 Article, US'032, US'924 and Martin 1987 Article cited by all the opponents for the ground of obviousness either alone or in combination render the claimed invention as obvious. Further, all the above documents have been cited in the specification as prior art documents.

36. The genus disclosed in the U Beauchamp in 1992 article discussed about toxicity associated with phosphorylation of the unconverted prodrug and a stereo-specific transporter which may contribute to the improved absorption of the amino acid in the prodrug esters, more particularly L-amino acid esters were better prodrugs that the corresponding D- or DL-isomers. In 1993 article of Beauchamp again reiterates about the toxicity

associated with the phosphorylated forms of the unconverted prodrugs. US '032 disclose ganciclovir, but there was no information on bio-availability related information, particularly oral bioavailability of monoesters of ganciclovir.

37. US'339 discloses only the di-esters wherein the preparation involves utilizing three-fold excess of the activated amino acid and the monoester would not be expected to be formed using the said six procedures in six examples. Example 6b describes a process for preparing bis-ester of an alaninate as a desired product with 10% of monoester as impurity. There is no motivation or suggestion whatsoever to make mono L valine ester of ganciclovir in US'339. US '924 relates to L valine ester of acyclovir, which does not teach about ganciclovir or esters of ganciclovir. Combining the teaching of Beauchamp's publication 1992 and 1993 with US '924, a person ordinarily skilled in the art will be motivated to block all the free OH group resulting in bisester.

38. The counsel further argued that the opponents cannot selectively choose the file wrapper of one country. The corresponding patents of '232 were filed in over 60 jurisdictions and it has been granted in over 50 jurisdictions. The nature and scope of the present claims in other countries including EP is very much similar to Indian patent '232. Therefore, it would be illogical for the opponents to rely only on the file wrapper of the US application. None of the documents either alone or in combination teach or suggest or enable a process for selective esterification of ganciclovir to obtain a prodrug having high oral bioavailability for ganciclovir that maintains the antiviral characteristics of ganciclovir. It was found by the present inventors that the monoesters of L-valine amino acid of ganciclovir are far more bioavailable than the bis-ester and despite Beauchamp's teaching away from the said monoester and despite its chirality which leads to existence of diastereomers it was a preferred compound. Thus the claimed invention possess inventive step and is non-obvious.

39. Section 2(1)ja defines "Inventive step" as follows:

> "Section 2 (ja) "Inventive step" means a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art;"

40. I agree with the counsels for the opponents that the nucleosides such as acyclovir, penciclovir are low aqueous solubility and low bioavailability when administered orally. To increase the oral bioavailability many modifications were done to purine ring and acyclic side chain, interestingly, ester of the said molecules shown improved bioavailability. Many esterifying agents were used and tested. Conversion of acyclovir into L-valine ester of acyclovir is suggested by '924 patent, such a modification makes the molecule more bioavailable than the base. The '329 patent discloses di- valyl amino acid ester of ganciclovir. The problem associated with the ganciclovir is poor solubility and low oral bioavailability. The prior art suggests that many similar nucleosides are converted into ester of amino acids, preferably L-valine to increase the oral bioavailability.

41. I am in an opinion that the comparative table shows the improvement in oral bioavailability of the esters of ganciclovir in example 9 of the specification is not proper. The comparison would have been made with the hydrochloride salt of other esters and monovaline ester of ganciclovir listed in the table. It is obvious that the solubility of salt, particularly hydrochloride salt is comparatively more to that of esters listed therein. Generally, esters are fairly soluble in water but salt of the ester is more soluble than the ester. Therefore, the comparison made between esters and salt in the table as an improvement with regards to bioavailability is not scientific and the results provided are not proper to meet the patentability requirement. There is no comparison between base and the salt. Since the object of the invention is to provide a prodrug of ganciclovir with improved oral bioavailability, the comparison provided in the specification to show such an improvement is not scientific. Thus the

applicant failed to provide a proper support in the complete specification for improved oral bioavailability.

42. The improved oral bioavailability of valganciclovir may be due to the addition of the L valyl ester, which allows the molecule to be actively transported but the salt form plays important role to influence the transportation. Most of the drugs listed in the pharmacopoeias are in the salt form, because the salt form of the drugs influences the solubility for better therapeutic effect.

43. The preferred ester forming compounds suggested by '329 patent and '924 patent are amino acids, particularly valine, more particularly L-valine to overcome the problem of oral drug delivery.

44. Beauchamp suggests and motivates the involvement of stereospecific (L- vs D-) transport process using common branched chain amino acids, L-valine and L-isoleucine, particularly L-valine ester which makes the drug more oral bioavailble.

In **Pfizer v. Apotex (U.S.Court of Appeal, 20061261)**, observed that for the test of obviousness only a reasonable expectation of success and not a guarantee is needed.

In **Aventis v. Lupin (U.S.Court of Appeal, 20061530)** the court held that "where the prior art gives the reason or motivation to make the claimed compositions, creates a prima facie case of obviousness."

45. The skilled person would have been motivated to prepare mono L-valine ester of ganciclovir from the teachings of the '329, '924 and the Beauchamp articles. Therefore, Claim 1 and dependent claims are not inventive.

46. Neither '339 patent nor '329 patent specifically mentioned the process for the preparation of the compound of the claimed invention. Identification of the compound of the invention from '329 is obvious, but the method for the preparation of such a compound requires extensive research work. Even though the method for hydrolyzing one of the ester group of '329 patent or any other steps involved in the preparation is by conventional method it could not have been ascertained before it was produced. Therefore I allow the process claim(s) but restricted to single process.

6. Not an invention

47. The counsels for the opponents argued that the compound claimed in claims 1-9 and 12 relates to a new form of a known substance which is already disclosed in US '339 patent. Data provided in the complete specification is an alleged increase in bioavailability of acetate and hydrochloride salts of the L-monovaline ester in rats and monkeys wherein the increase in bioavailability in not sufficient to meet the requirement of significant enhancement in therapeutic efficacy. The table provided in example 9 of the specification with bioavailability data did not provide any comparison between salt and base of valganciclovir. Therefore the comparative table is not proper.

48. Valganciclovir is a prodrug of ganciclovir, however, the pro drug is also used for the purpose for which original drug is used. Acyclovir and L-valine-ester of acyclovir, i.e., valaciclovir are antiviral drug of similar class is also known in the art. Prodrug will be developed in order to enhance the bioavailability when given orally. The prodrug achieves the same as that of the drug.

49. Ester of the known substance prima facie will get a patent only if it shows significant enhancement of efficacy. The Hon'ble High Court of Madras in Novartis Judgment held the constitutional validity of section 3(d) as categorically that efficacy means therapeutic efficacy followed by IPAB

judgment. In the present case, mono ester demonstrated to have more bioavailability compared to that of bis ester of ganciclovir that is not considered as efficacy. The Hon'ble IPAB had also stated that 'Efficacy' and 'bio-availability' are two different concepts and are not the same. The Hon'ble IPAB has also stated that this difference is also proved from the definition of efficacy, which states that therapeutic effect is independent of property (i.e. bio-availability). Claim 4 is not clearly and particularly described and in the absence of any improved effect the crystalline form considered as another form of a known substance u/s 3(d) of the Act.

50. Since claim 1 is not novel and inventive, making a composition of known drug with known excipients cannot be considered as an invention. Therefore, claim 9 is a mere admixture resulting only in the aggregation of the properties of the components thereof.

> Section 3 (d): the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.
>
> Explanation to Section 3 (d): "Salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations, and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.

51. The counsels for the opponents further argued that the complete specification does not disclose any synergistic effect for the substance with a pharmaceutically acceptable excipient or carrier material. Therefore, claim 9 falls under section 3(e) of the Act.

52. The counsel for the patentee submitted that valganciclovir is not only more "efficacious" having regard to compounds known for treatment of CMV but even "therapeutic" and "curative". The enhancement in oral bioavailability has resulted in direct control over dosage administered to the patient, thereby minimizing the risks associated with prior art intravenous treatments, particularly for immune compromised patients as well as reduction in any side effects that the drug molecule itself may cause in a patient due to over dosage.

53. Further the counsel referred Per Ljungman's affidavit which explains in detail about the effects of low resistance, no mutations, and systemic exposure, which are achieved by valganciclovir and in paragraph 40,

> "Valganciclovir has a bioavailability of approximately 10 times that of oral ganciclovir, with one daily dose of 450 mg of valganciclovir giving a similar area under the concentrative curve (AUC) as Ig three times daily of oral ganciclovir. In contrast to oral ganciclovir, the systemic exposure increases with the dose of valganciclovir. The maximum concentration when given in one daily dose of 900 mg is typically 5-6 mg/ml and the AUC up to twice what can be achieved by oral ganciclovir given 3 times/day. "

In paragraph 23 at page 9 of the said affidavit equates the increased bioavailability of valganciclovir with the positive existence of clinical efficacy in the following words:-

> "Clinical efficacy results from many important aspects of both the chosen drug and the status of the treated patient. Important aspects of the drug influencing clinical efficacy include the side effect profile, bioavailability, and drug interactions. Clinical efficacy is also influenced by the concentration of the antiviral drug that can be delivered to the relevant site of infection or disease, such as through the blood for preemptive therapy or into the eye for treatment of CMV retinitis. Examples of patient factors influencing clinical efficacy are gut graft-vs-host diseases that can influence absorption of an oral drug

and the degree of immune-suppression of the patient. The more severely a patient is immune-suppressed, the more difficult it is to effectively decrease CMV replication.

54. The counsel further submitted that the bioavailability and therapeutic efficacy are not one and the same but closely related in such a way that one affects the other. The increased bioavailability is a property and the effect of the same is low resistance, no mutations, system exposure and avoidance of the drawbacks of the intravenous treatment which are nothing but therapeutic efficacy as explained in Per Ljungman affidavit, particularly in paragraphs 30 to 48 .

55. The counsel submitted that opponent's argument on the comparative data provided in Example 9 of the specification for the oral bio availability cannot be accepted since valganciclovir is in hydrochloride or acetate salt form where as ganciclovir and bis esters are not in salt form do not contain any merit. All bioavailability experiments for mono esters of '232 patent were conducted with either the hydrochloride or the acetate (salt of acetic acid) salts, which was done for chemical stability reasons. In fact, the improved oral bioavailability of valganciclovir is not because of the particular salt form, but due to the addition of the L valyl ester, which allows the molecule to be actively transported and is not dependent on the particular salt form or the solid state characteristics of the molecule.

56. Claim 9 is directed to a composition comprising a novel and inventive compound, which is being a dependent claim, derives novelty and inventive step from the compound claimed in claims 1 to 8. Hence, claim 9 does not fall within the scope of Section 3(e) of the Patent Act.

57. I agree with the arguments of the counsels for the opponents that the oral bioavailability is not therapeutic efficacy under the provisions of the Act. Data provided in example 9 of the specification is pertaining to the bioavailability, but not for the therapeutic efficacy. The improved bioavailability may increase the clinical efficacy in turn it may influence the therapeutic efficacy for which there is no support is provided in the specification. Clinical efficacy and therapeutic efficacy is not considered as

one and the same, but it is different. In general, it is obvious that the prodrug of compound exhibit improved solubility, low resistance, no mutations, system exposure and avoidance of the drawbacks of the intravenous treatment which are inherent and expected properties of the prodrug. The composition claimed in specification is a mere statement without any scientific work or without any support showing synergistic property. Therefore the compound and its pharmaceutically acceptable salts, isomers, crystalline form and composition do not fulfill the requirement under the provision of the Act.

7. Statement and undertaking regarding foreign applications

58. The counsels for the opponents argued that the applicant failed to furnish the information required under section 8 of the Act. The patentee filed Form 4 on 27-7-1995 declaring only US Patent Application No.08/281893 as a corresponding foreign application pending and Annex to Form 4 was filed on 8-6-1996, but still further information about foreign filing on 23-05-2006 which was beyond the time limit. It is evident from the application data and transaction history of US Patent Application No.08/281893 available in the website of USPTO that a non-final rejection had been mailed on 16-6-1995, over a month before the filing of the present application. Annex to Form 4 submitted subsequently on 8-6-1996 lists US Patent Application No.08/281893 as 'pending', whereas the application was abandoned on 16-6-1995. Therefore the patentee has furnished false information.

59. The counsel for the patentee submitted that the all the relevant information required under the said section 8 have been submitted to the Patent Office. Accordingly, no false information has been submitted pertaining to the status of the application filed in other jurisdictions.

60. Section 8. (1) Where an applicant for a patent under this Act 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, or where to his knowledge such an application is being prosecuted by some person through whom he claims or by some person deriving title from him, he shall file along with his application-

(i). a statement setting out detailed particulars of such application is being prosecuted, the serial number and date of filing of the application and such other particulars may be prescribed; and

(ii). an undertaking that, up to the date of the acceptance of his complete specification filed in India, he would keep the Controller informed in writing, from time to time, of details of the nature referred into clause (a) in respect of every other application relating to the same or substantially the same invention, if any, filed in any country outside India substantially the same invention, if any, filed in any country outside India subsequently to the filing of the statement referred to in the aforesaid clause, within the prescribed time.

Rule 13 (1) Statement and undertaking regarding foreign applications.-

(1). The statement and undertaking required to be filed by an applicant for a patent under sub-section (1) of section 8 shall be made in Form 4.

(2) The time within which the applicant for a patent shall keep the Controller informed of the details in respect of other applications filed in any country outside India in the undertaking to be given by him under clause (b) of sub-section (1) of section 8 shall be three months from the date of such filing.

61. The ground for opposition under section 25(2) (h) of the Act as follows:

(i). the patentee has failed to disclose to the Controller the information required by Section 8, or

(ii). has furnished the information which in any material particular was false to his knowledge.

62. Photocopy of the prosecution history of US application which is taken from the website of the USPTO submitted during the proceedings as evidence not an authenticated document, therefore it is not considered. Different countries have different provisions in different jurisdictions. The patentee has met all the requirements under the provisions of the Act during prosecution of the application.

8. Locus standi

63. The counsel for the opponents (5) and (6) submitted that the provision includes an organization representing persons living with HIV and come within the meaning of section 2(1) (t) of the Patents Act and has locus to file this post-grant opposition, especially in valganciclovir.

64. The counsel for the patentee argued that DNP+ has no manufacturing, trading or research interest and is, therefore, not a person interested within the meaning of Section 25(2) of the Patents Act, 1970. It is stated that under Section 25(2), the language used "person interested" as opposed to Section 25(1) which uses the language "any person". The person interested must be a person with a direct tangible commercial or research interest. The person must have, therefore, either a manufacturing, trading or research interest or must own patents in the field or must suffer some threat, injury or otherwise had affected by the presence of the patent.

65. The provision of the Act as follows:

2(t) "person interested" includes a person engaged in, or in promoting, research in the same field as that to which the invention relates;

In **Ajay Industrial Corpn. Vs Shiro Kanso, AIR 1983 Delhi, 496,**

"In our opinion, a 'person interested' within the meaning of section 64 must be a person who has a direct, present and tangible commercial interest or public interest which is injured or affected by the continuance of the patent on the register."

66. DNP+, in my opinion, is a person affected or injured and well within the provision of section 2(1) (t). The transitional word 'including' is open term, which 'including the persons provided therein but not excluding others'. Therefore, I allow DNP+ as an opponent in the present case.

9. Conventional application

67. The counsels for the opponents contented that the application has to be made within twelve months from the date of filing of the application in a convention country. This application claims priority date from patent application No.08/281893 filed at the USA on 28-07-1994. U.S.A. was not declared as a convention country by India at the time of filing of the basic application. Section 135 of the Patents Act strictly requires this. On 28-07-1994 when the basic application was filed in U.S.A. it was not a convention country. Only by a notification issued on January 3rd, 1995 U.S.A. was declared as a convention country. Indian Patents Act does not protect product patent of drugs before 1st January, 1995 and so this alleged invention is not valid. The counsels referred the Daniel AC v/s. Controller of Patents.

68. The counsel for the patentee submitted that the ground of opposition by way of application for amending the notice of opposition and statement of opposition filed on 3rd April 2009, which was filed much after the prescribed time period of one year from the date of publication of grant of patent that expired on 29th June 2008. Thus, the amendment should not be allowed.

69. The counsel for the patentee refers to the Controller's decision in **Eli Lilly & Co. vs. Ranbaxy Laboratories Limited in respect of Indian Patent Application No. 85/DEL/1995 where the Controller held the following:**

> "I find that as such the issue of validity of priority does not fall within the ambit of any grounds of opposition as stipulated in Section 25(1) of the Patents (Amended) Act, 2005. Needless to mention that the applicant & opponent are required to limit their submissions only on the grounds specified u/s 25(1) (a) to 25 (1) (k) but on no other ground"

The grounds of pre-grant opposition provided under Section 25(1) are identical to the grounds of post-grant opposition provided under Section 25(2). Hence, the intervener's arguments or submissions do not fall within the ambit of the ground specified under Section 25(2) (i).

70. USA had been notified as convention country well before the date of filing of this application in India. In Novartis decision, the respondents objected to the grant of priority date to Novartis as Switzerland being the basic country was not a convention country on the date of filing of the application. The IPAB held as follows:-

> "In the decision dated 07.09.2005 in the case of **Agouron Pharmaceuticals Inc. V Controller of Patents in the High Court at Calcutta (special jurisdiction. Original side) (AID NO. 2 of 2001) Hon'ble S.K. Mukherjee, J** has observed "it is well settled that the appellate court is entitled to take into consideration any change in law and give proper relief on that basis". Accordingly, we do not agree with the arguments of the respondents and find that the appellant is fully justified and entitled to get the convention priority date 18.07.1997 under the amended section 133 of the Act. Provision of section 6 of General Clauses Act, 1897 does not apply here as the original Act has not been repeated. "

71. Further the counsel contented that the Calcutta High Court order of Justice **Ruma Pal in Daniel vs Controller of Patents** will not be applicable to the present case because the order was under Section 15 of the Patents Act and not under the ground of opposition of Section 25 and section 133 of the Patents Act has been amended since then the order is passed. Therefore, this ground of opposition is not maintainable as on the date of filing of the application in India, US was a convention country under Section 133 of the Indian Patents Act.

72. I am in an opinion that US was a conventional country when the application was filed in India. Even though Government of India notified US as a conventional country after the filing date of the US application, the door was opened for the applicant when the application was filed in India. Nowhere in the Patent Act mentioned that the invention relating to product carried out or application filed before 1995 are not patentable. Therefore I allow the conventional status of the present application.

73. I agree with the counsel for the patentee that new ground of opposition by way of amending much after prescribed time limit not allowed.

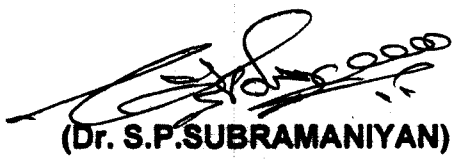
> **Kawal Singh Akbar v. Baldeo Singh Akbar, AIR 1957 Nagpur 57, the Nagpur High Court held:** "It was held that the application to take the additional ground should be treated as a new application to set aside the award and must be dismissed as it was barred by limitation. No quarter can, therefore, be given to the latches and delay, which the appellant has been guilty of".

74. The additional ground added to the opposition is not allowed.

75. I have not considered any other ground filed by way of opposition in this case, which is irrelevant.

76. In view of the discussion in the preceding paragraphs, considering the relevant arguments put forward by the Counsels for the opponents and counsel for the patentee at the hearing, the documents on record and the relevant written submissions made by all the parties and all the circumstances of the case, the post-grant opposition filed by the opponents under section 25(2) of the Act is accordingly order to amend the patent to process claims restricted to single process, if the patentee wish to proceed, can make a request within 15 days from the date of receipt of this decision.

Dated this 30th day of April, 2010.



(Dr. S.P.SUBRAMANIYAN)
Assistant Controller of Patents & Designs