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LAKSHMI KUMARAN
&
SRIDHARAN

September 21, 2009

The Controller of Patents,
The Patent Office,
Intellectual Property Rights Building
GST Road, Guindy
Chennai– 600 032

Kind Attn: Mr. S. P. Subramaniyan Assistant Controller of Patents & Designs

Dear Sir,

Sub: Written submission subsequent to hearing held on August 4 and September 8, 2009

Ref: In the matter of Post-Grant Opposition filed by Ranbaxy Laboratories Ltd. against Patent No. 207232 filed by La-Hoffmann Roche

The undersigned along with Mr. Ayush Sharma and Dr. Lunalisa Potsangbam appeared, on behalf of the Opponent, before the Ld Assistant Controller on August 4 and September 8, 2009. The undersigned argued the matter on 4th August. On September 8th the applicant replied to those submissions, followed by the rejoinder of the Opponent. At the conclusion of the hearing, the Learned Assistant Controller was pleased to direct the parties to file their written submission on or before September 18, 2009. Accordingly, this written submission is made.

1. At the outset, it was submitted that the grounds contained in the Opposition dated 23rd January, 2008 and reply evidence dated 8th July, 2008 are to be taken as reiterated. It was submitted that all the product claims were still under opposition and it is only

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the process claims that are not being opposed consequent on amendment to the process claims. At the oral hearing, specific submissions were highlighted.

2. The said Opposition was made on the following grounds:

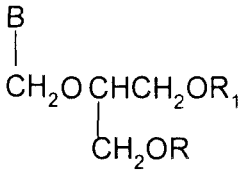
2.1. The subject matter of the Patent is not novel in view of EP '329 Patent read with the Supplementary Protection Certificate issued to EP '329 for Valganciclovir;

2.2. The subject matter of the Patent is obvious in the light of the existing prior arts; and

2.3. The subject matter of the Patent is not an invention as per Section 3 (d) of the Patents Act, 1970.

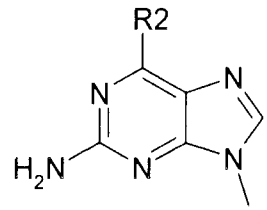
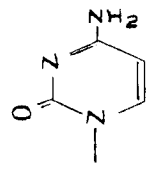
3. On <u>Anticipation</u>

3.1. EP 0375329A2 discloses compounds of formula (I) for the treatment of prophylaxis of virus infection, especially herpes infections (Page 3, line 11 to 14). It further discloses that amino acid esters of ganciclovir are preferred by virtue of their especially improved bioavailability in comparison with the parent compounds (ganciclovir). (Page 2, line 54 to 55)



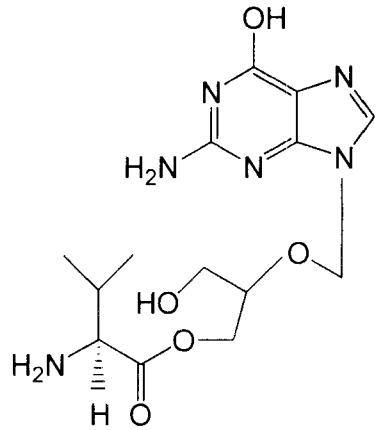
Formula I

3.2. This formula I has three variable groups (B, R_1 and R). Groups R and R_1 can be independently selected from hydrogen atom and an amino acid acyl residue providing at least one of R and R_1 represents an amino acid acyl residue (Page 2, line 30). It also discloses that group B in formula I represents a group of formula (purinyl derivative and pyrimidinyl derivative as shown below) (Page 2, line 31) in which R_2 represents a C1-6 straight chain, C3-6 branched chain or C3-6 cyclic alkoxy group, or a hydroxyl or amino group or a hydrogen atom:

B =  or 

Purinyl derivative Pyrimidinyl derivative

3.3. Replacing in the formula I, group B with the purinyl derivative, group R or R_1 independently with hydrogen atom and at least one of R or R_1 representing an amino acyl residue having aliphatic amino acid, most preferably an L-amino acid (e.g. L-valyl) (Page 3 line 1 to 6) and R_2 with an –OH group, arrives at a compound of the formula below:



3.4. Thus, it is clear that the compound of the above-mentioned formula is the same as the compound of formula claimed in claim 1 of Patent No. 207232.

3.5. The '329 patent also discloses that the amino acid esters according to the invention include the mono- and di-esters of the compound of formula (I) (Page 3, line 5). Further, the Patent itself admits that it is apparent from formula (I) that the compound has one asymmetric carbon atom (chiral center) in the propanyl chain, in addition to the asymmetric carbon atom in L-valine. Therefore, two diastereomeric forms exist, the (R)- and (S)- form as determined by the rules of Cahn et al. (Page 39 line 13 to 18). Further, it also states that the amino acid according to the invention includes the mono- and di-esters of the compound of the formula (I). The amino acids may be D- L- and DL amino acids, with the L- amino acids being most preferred (Page 3, line 4 to 6).

3.6. In Para 4.8 of the reply, the Patentee has accepted that '329 patent *contains broad genus of molecules.* It was submitted by the Patentee during the hearing that '329 Patent consists of a genus of about 492 compounds and not 18 as asserted by the opponent. They argued that the 18 compounds were according to the later publication (EP 0375329B) and hence cannot be considered. Even if this argument of the Patentee is presumed to be correct, the size of the genus of '329A will not be 492 compounds, as submitted by the Patentee but only 24 compounds. This is because the earlier publication ('329A) gives a clear direction that the *preferred amino acids include glycine, alanine, valine and isoleucine* (page 3 lines 3 and 4 of the '329 patent). It further indicates that the *amino acid esters include mono- and di-ester of the compound of formula (I)* (Page 3, line 5). Further, *L amino acids are disclosed as the most preferred isomer*(page line 6). Hence, the person skilled in the art would have limited options to try these four preferred L amino acids resulting in only 24 compounds. The 24 compounds form a very small genus anticipating the species claimed by the applicant. Further, in the prosecution of the corresponding US patent application (now granted as US 6083953) of **Patent No. 207232,** the US Examiner had cited the '329 Patent an anticipating prior art document since it taught a small genus of compounds. This argument of the US Examiner was not rebutted by the Patentee as evidenced by the action of amending the claims to *crystalline form.* Hence, it is very clear that EP '329 anticipates the Indian Patent. The Opponent relied upon the case of *In re Martin Gleave* to show that even a genus of 1400 sequences listed in the prior art anticipates one single sequence. In *Martin* the prior art (Wraight patent) did not teach the utility of the sequences nor any of the sequences in the prior art was actually made and tested. US Federal Circuit stated that for anticipation – no actual creation or reduction to practice is required (Page 5). Further, The Federal Circuit stated that *"it is not necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement*" (Page 12). The Patentee argued that in order to anticipate, a prior art must enable the claimed subject matter. It is very clear from the *In re Martin Gleave* that to satisfy the enablement requirement for anticipation the prior art need not have made or disclosed the utility of the claimed compound. The Opponent also relied upon the judgment of *In re Petering* to state that small genus anticipates the single species.

3.7. Hence, in the light of the above submissions, it is very clear that a small genus as disclosed in EP '329 patent will anticipate the claimed subject matter of '232 Patent. This is so irrespective of whether the genus was 18 or 492.

3.8. It is also to be noted that example 5 of EP'329 teaches a *bis-(L-valinate) ester of ganciclovir* and example 6(b) teaches that by the process enunciated in that example, a person would get *mono-(L-alaninate) ester of ganciclovir along with bis-(L-alaninate) ester of ganciclovir in the ratio of 1:9. The example also discloses that the formation of the compounds was confirmed by H-NMR and C13-NMR, amongst other spectral studies.* It is very clear from example 6(b) that the monoester was prepared and isolated, as evident by the H-NMR and C13-NMR analyses. It is to be noted that the formation of a mono or a bis-ester depends on the relative amounts of the amino acid employed in the reaction and this fact is supported by the submissions of Patentee in Para 4.11 of its reply. Patentee submits that in *all examples of EP'329 a three-fold 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. Since the mono-ester will be lower molecular weight than the bis-ester, as described in the above process, *it may be isolated in a conventional manner, i.e.,* by chromatographic techniques.

3.9. In any event the skilled reader will readily appreciate that the mono-ester will be formed by selectively protecting either hydroxyl group and then esterifying the unprotected hydroxyl group, the esterification step being performed as described in EP'329 (Page 5, line 21) or by use of selective hydrolysis of the bis-ester product to form the mono-ester. Both the techniques would be within the grasp of the skilled reader and can be applied without undue burden.

3.10. Thus, in EP '329 patent, there is enough information pertaining to mono-ester of ganciclovir and a skilled reader does not have to exercise intellectual efforts to arrive at the claimed compounds of Indian Patent 207232.

3.11. It was also pointed out by the Opponent that in United Kingdom, a Supplementary Protection Certificate has been granted to EP '329 patent for Valganciclovir hydrochloride, wherein the applicant (Glaxo) claims that the product, and/or the UK authorized medicinal use thereof (treatment of cytomegalovirus retinitis in AIDS patients) and/or formulation thereof and/or synthetic methods thereof, are covered by at least claims 1, 2, 5, 6, 7, and 9 to 14 and possibly claim 8. This certificate makes it clear that valganciclovir is disclosed and enabled by EP'329 as no patent will be granted unless there is sufficient disclosure and enablement of the claimed product. Thus, EP'329 patent anticipates the invention as claimed in patent 207232. The SPC supports the contention of the opponent which was based on first principles, starting from the '329 patent. It is clear from Annexure 3 of Opponent's reply that the applicant of EP'329 patent had admitted that all marketing authorization information about the product was with Roche and the applicant sought the information from Roche itself (Page 1, line 5 to 8). Therefore, the Patentee (Roche) was aware of the fact that SPC was granted to EP '329 patent for valganciclovir hydrochloride in Europe and the Patentee has suppressed this material fact from the Patent Office.

3.12. The Patentee relied upon the judgment of ECJ in the case of *AHP Manufacturing* v *Bureau voor de Industriele* C-482/07 and argued that two SPCs can be given for the same product. This judgment relates to the issue whether an SPC can be granted to a product when another SPC was pending for the same product. This issue arises in a case where the same product is covered by two or more patents granted to different parties, as for example, patents covering product claim or process claim or use claims for the same product. The ECJ held that if a product is covered by two or more basic patents granted to different parties, then SPC can be granted to each party only for one patent. The ECJ gave this judgment keeping in mind the different practices adopted by different EU members regarding issuance of SPCs. It is very clear from the handout provided by the Patentee that a basic patent can be for either product, process or use claims (Page 2). This clearly shows as to how a product can be covered by more than one patent and as to why SPCs can be granted to all the patents granted to different parties. The situation in the present case is totally different as both the

patents have product claims and thus, this judgment is not applicable in the present case.

3.13. It is submitted that 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. It is submitted that the Patentee during the prosecution in United States amended the claims which were originally as that of Indian Patent to overcome the objections raised by Examiner in view of US 5,043,339 (corresponding US Patent of EP '329) to *crystalline form*. Examiner stated that the as-filed claims (same as Indian granted) were anticipated by US '339 (EP'329) Patent as it teaches a small genus of compounds and hence each member of the genus is considered as anticipated. Patentee did not contest this and to overcome this objection the Patentee has amended its claims to *crystalline form*. This also supports the Opponent's submission that EP '329 anticipates the claimed invention. It is also relevant to note that the Patentee filed three continuation applications of US Patent 6,083,953, in an attempt to get claims on valganciclovir hydrochloride granted, but abandoned them all because the Examiner would not allow such a claim.

3.14. The Opponent has provided ample evidences to establish that the subject matter of the patent 207232 is anticipated by the disclosure of EP '329 Patent; which is further affirmed when read along with the Supplementary Protection Certificate (SPC) issued to EP '329 Patent and the Prosecution history of corresponding US application of Indian Patent 207232.

4. The subject matter of the claimed invention is not an invention

4.1. The subject matter of the invention relates to *mono-(L-valinate) amino acid ester of ganciclovir*. The Patent admits that bis-(L-valinate) amino acid ester of ganciclovir was known in the prior art and was a more preferred drug over the parent drug (Page 5, line 23 to 24).

4.2. Example 9 of the Patent discloses the bio-availability of the various compounds (table provided under example 9). It discloses that bio-availability of G-bis (L-valine) ester (Bis-valine ester, EP '329 Patent) is 52.0% whereas the bio-

availability of G-L-valinate hydrochloride (mono-valine ester hydrochloride) is 98.1%. It is submitted that this table discloses the bio-availability of hydrochloride salt of G-L-valinate and not of G-L-valinate ester, i.e., this table does not disclose the bio-availability of the claimed compound and it is not proper to compare the bio availability of the bis-ester with the hydrochloride salt of the mono-ester. Hence the specification lacks the disclosure regarding the bio-availability or efficacy of the claimed invention.

4.3. Efficacy as defined by Dorland's Illustrated Medical Dictionary is the ability of a drug to produce a desired therapeutic effect; it is independent of potency, which expresses the amount of the drug necessary to achieve the desired effect. This definition is in medical dictionary and hence is understood accordingly by the persons involved in the relevant art. The Hon'ble Madras High Court and Intellectual Property Appellate Board (IPAB) have adopted this definition with regard to chemical inventions. IPAB had stated that *the term "efficacy" has already been defined by the Madras High Court in its decision (supra) as "therapeutic effect in healing a disease or having a good effect on the body" taking into consideration of legislative intent for introduction of this provision in the patent law amended in such a fashion so as to avoid proliferation of patents around existing pharmaceutical products and to prevent "evergreening" by creeping in a new standard of novelty and inventive step in the patent law for such products attaching a tag of "efficacy". We also respectfully agree with the observation of the Hon'ble Court.* 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).* It also held that bio-availability is not the same as therapeutic efficacy. The Patentee stated at the hearing that the IPAB judgment is correct in law and is binding on the Controller. It is noteworthy that the draft Manual of Patent Procedures and Practice (2008) published by the Indian Patent Office also states the same position (page 58, Section 4.5.6).

4.4. It was pointed out by the Opponent at the hearing that there is not even an iota of evidence in the specification regarding the efficacy of the substance. The specification and all the experts (including Ljungman's affidavit - cited by

Patentee) states that the hydrochloride salt of mono-valine ester has bio-availability of about 98.1%. None of the affidavits states the bio-availability of mono-L-valine ester (the claimed compound), leave alone about the efficacy of the ester or the salt vis-à-vis the known substance (bis-ester). It was also pointed out that the specification does not disclose the efficacy of the claimed compound (mono-L-valine ester) nor do any affidavits disclose the efficacy of the claimed compound. Ljungman's affidavit (Para 48) states that the claimed compound has efficacy but the statement is without any evidence. Thus, such a baseless statement of Per Ljungman cannot be relied upon. Hence, the Patentee had failed to prove significantly enhanced efficacy of the claimed substance vis-à-vis the known substance (Bis ester).

4.5. It was argued by the Patentee that in order for a substance to become a *known substance,* a compound should be commercialized in the market and since bis-ester was never commercialized in the market, it cannot be considered as a known substance for the purpose of section 3 (d). The Patentee did not provide any evidence or material to support this argument. The Opponent refuted the argument as it is not necessary that the compound should have been commercialized. No such requirement can be found in section 3(d) either explicitly or by necessary implication. In fact the patent admits that bis-(L-valinate) amino acid ester of ganciclovir was known in the prior art and was a more preferred drug over the parent drug (Page 5, line 23 to 24). Thus, it is clear that the bis-ester was the more preferred drug and hence the efficacy of the mono ester should have been disclosed with reference to that preferred drug (known substance) -the bis-ester - to overcome section 3 (d). This burden has not been discharged by the applicant.

4.6. Thus, it is clear that the Patentee has not shown any data regarding increased therapeutic effect of the mono-(L-valinate) amino acid ester of ganciclovir over bis-(L-valinate) amino acid ester of ganciclovir or even with reference to ganciclovir in the patent application. Hence, the claimed subject matter is not an invention within the meaning of the Patents Act.

4.7. In reply, the applicant pointed out that while under pre-grant opposition the burden of proof was on the patentee, in the case of post-grant opposition the burden was on the opponent and referred to sections 101, 102 and 103 of the Indian Evidence Act. The opponent pointed out in rejoinder that both in pre-grant and post-grant oppositions the initial burden was on the opponent and in support referred to Rule 55 on pre-grant opposition and Rule 58 on post-grant opposition. This submission appears to have been twisted and stated at the hearing of the next opponent that burden of proof has been conceded to be that of the opponent. There is no need for any concession on a legal point. The opponent in this case has made out a clear case under section 3(d). It is an undisputed position that the mono ester now claimed is the same substance as per explanation to section 3(d). The only point of dispute is whether the known substance is ganciclovir or bis-ester of ganciclovir, which has no impact on the burden. The term efficacy has already been defined by two higher judicial fora, which is binding on the Controller, to be therapeutic efficacy in the case of pharmaceuticals. The IPAB has categorically held that bio-availability is not efficacy. The opponent had also placed on record the Dorland's dictionary and the book Goodman and Gilman to show efficacy is different from potency and how enhanced efficacy is depicted. Thus, the initial burden has been more than discharged. The burden there after shifts to the patentee who has not discharged his burden.

4.8. The Patent does not disclose the efficacy of Valganciclovir (mono-valine ester of ganciclovir) vis-à-vis ganciclovir or its bis-ester;

4.9. Example 9 only discloses the bio-availability of G-L-valinate hydrochloride and not the bio-availability of G-L-valinate ester (mono-valine ester of ganciclovir-claimed product). In any case bio-availability is not efficacy.

4.10. The comparison provided under table 9 is erroneous as it compares the bio-availability of ganciclovir or its bis-ester with hydrochloride salt of the mono-ester.

4.11. It was conceded by the Patentee that bio-availability and efficacy are not same but two different concepts.

4.12. The Madras High Court in the case of Novartis v Union of India stated that "If a discovery is made from a known substance, a duty is cast upon the patent applicant to show that the discovery had resulted in the enhancement of a known efficacy of that substance".

4.13. In the light of the above submissions the Opponent has discharged its burden of proving its case of invalidity and the burden had shifted to the Patentee to prove that the Patent is valid.

5. The subject matter of the claimed invention is obvious

5.1. The Patent admits that acyclovir, which was the first drug, having good activity against herpes viruses is known in the prior art (Page 2, line 15 to 22). It further admits that L-valyl ester of acyclovir was the best prodrug out of 18 amino acid esters which were investigated by the scientists. These amino acid esters were tested for anti-viral activities. (Page 9, line 3 to 25). It further discloses that ganciclovir is highly efficacious against viruses of the herpes family and is known in the prior art. (Page 2, line 24 to 31).

5.2. According to EP '329, the amino acids of ganciclovir are preferred medicines for herpes because of improved bioavailability in comparison to the parent compound (Page 2, line 54 to 55). Further, it also states that the amino acid esters according to the invention include the mono- and di-esters of the compound of the formula (I). The amino acids may be D- L- and DL amino acids, with the L- amino acids being most preferred (Page 3, line 4 to 6). Further, EP '329 discloses the preparation of bis-(L-valinate) ester of ganciclovir as a solid (Page 5, line 23 to 24). This bis-(L-valinate) ester of ganciclovir is also known to have an activity against the herpes infection. Further, it is submitted that mono-acyl derivative ester of ganciclovir is also known in the prior art. (Example 6(b)).

5.3. It is wrong to state that mono-alaninate ester (Example 6b of EP'329) is an *impurity*. The example discloses that on analysing the compound obtained by the process by ^{1}H NMR, ^{13}C NMR, HPLC and Mass spectra, it was proved that the compound was a mixture of mono and bis alaninate. It is well known in chemistry that ^{1}H NMR, and ^{13}C NMR are performed only after isolation of compound and in a purified form. Thus, it is incorrect to state that EP'329 does not isolate the mono-ester.

5.4. In short it is submitted that the invention claims mono-(L-valinate) ester of ganciclovir having the activity against herpes viruses and the bis-(L-valinate) ester of ganciclovir is known in the prior art. Further, it was pointed out that Acyclovir had only one –OH group. It was also admitted by the Patentee that valyl ester of Acyclovir was a successful prodrug. In light of such teachings a person skilled in the art would try with only one ester in choosing the pro-drug.

5.5. It was argued strongly by the Patentee that Beuchamp 1992 and 1993 articles teach away from the claimed subject matter of the invention. Both these articles teach that toxicity of the congeners was hypothesized to be result of the phosphorylation of the unconverted prodrug. T his phosphorylation was hypothesized to be due to the presence of free hydroxyl group. It is well known that there is one free hydroxyl group present in valgancilocvir. Thus, according to the Patentee a person reading these articles would not try to work with the L-valyl ester of ganciclovir and hence there lies an inventive feature in their claimed invention. The Patentee relied upon the affidavit of Dr. Valentino Stella and Dr. Lester to support its argument.

5.6. It was pointed out by the Opponent that the scope of 1992 paper was to identify the best amino-acid ester of the antiherpetic drug acyclovir. The paper summarizes that 18 amino acid esters were synthesized and tested as potential prodrugs. The authors indicated that L-amino acid esters were better prodrugs than the corresponding D- or DL-isomers. It also stated that L-valyl ester, (256U87) was the best prodrug. The authors neither indicated nor concluded that there is a possibility of toxicity in mono-ester. The teaching of the 1992 and 1993 paper would have easily motivated any person skilled in the art to use L-

valyl amino acid ester to prepare the prodrug. Further, the hypothesis of 1992 article was a personal communication to another scientist and has no scientific implication for a person skilled in the art. This view is also supported by Opponent's affidavit of Dr. Gokel. Dr. Gokel states that the Beauchamp 1992 and 1993 papers taught that modifications can be made to purine antivirals to make them more bio-available and the best modification would be to make amino acid ester of purine antivirals, the hydrochloride salt of the L-valyl ester (Page 21, Para 47).

5.7. Further, it was also pointed out that in 1992 paper, it was stated that *since antiviral action is dependent on phosporylation of the parent compound (a fact which has been exhaustively documented), a priori, the intact esters, having no free hydroxyl group capable of phosphorylation, would not be expected to exhibit any antiviral action* (Page 161, Para 3). This appears to contradict the hypothesis of toxicity. This point is also well supported by Dr. Gokel in his affidavit (Page 24, Para 52-53). Further, 1992 paper reports a solution to the problem of oral bio-availability in acyclovir by making the hydrochloride salt of the L-valyl ester to use as a prodrug. A person skilled in the art would recognize the chemical and structural similarity between acyclovir and ganciclovir (Dr. Gokel's Affidavit – Page 25, Para 55). Further, Para 56 to 63 of Dr. Gokel's affidavit were also relied in this respect.

5.8. Thus, there was no clear teaching in the reading 1992 and 1993 papers directing the skilled person away from trying the mono-ester. Thus, mono-ester was the obvious thing to try.

5.9. Patentee further argued that Martin's paper teaches away from the invention as it teaches that monoester resulted in diminishing bio-activity. It was pointed out by the Opponent that the single mono-ester tested in the Martin paper was a "palmitate" ester. Palmitic acid used to form the palmitate ester is not an amino acid but a fatty acid ester. Thus, one skilled in the art would reasonably have attributed the poor results to the selection of the palmitate (which is a fatty acid ester and has poor solubility) and not because it was a mono-ester. In this respect, the Opponent relied upon the affidavit of Dr. Arvind Kumar Bansal (Page 10, Para 3).

5.10. The Opponent further relied upon an article of Dr. Valentino Stella (Patentee's expert) to show that the discovery and development of valganciclovir (claimed substance) was influenced by the observations made with valacyclovir (Opponent's additional documents dated 12.05.2009). This clearly shows that the study of valacyclovir gave way to the development of valganciclovir and hence the development was obvious in the light of the teachings of valacyclovir.

5.11. The Opponent further relied upon an article by Hans Maag (Co-inventor of the Indian Patent) where he has stated that *using the same prodrug approach as that for acyclovir, the valine ester of ganciclovir (valganciclovir) was identified as the lead prodrug based on marked increase in oral bio-availability* (Opponent's additional documents – dated 12.05.2009). This statement of co-inventor clearly indicates that the teachings of valacylovir motivated a person skilled in the art to work for valganciclovir. Thus, the claimed invention is obvious to a person skilled in the art.

5.12. Although both these articles are published after the priority date of the Indian Patent, yet these articles clearly serve to prove the point that the Opponents have made that the inventors of Indian Patent were taught and motivated by the science behind the development of valacyclovir as a successful prodrug of acyclovir when they developed valganciclovir as a prodrug of choice of ganciclovir. .

5.13. It was well known before the priority date of the Indian Patent that acyclovir, the first drug, had a good activity against herpes viruses. Various prior arts clearly teach that L-valyl ester of acyclovir was the best prodrug out of 18 amino acid esters which were investigated by the scientists. The Patent also admits this point. It was further known in the prior art that that ganciclovir was highly efficacious against viruses of the herpes family. The articles of Hans Maag (co-inventor of Indian Patent) and Dr. Stella (Patentee's expert) states that the development of valacyclovir was the motivation factor to use L-valyl ester to develop a pro-drug of ganciclovir. Thus, under such circumstances, the invention is obvious to a person skilled in the art and is liable to be revoked.

5.14. To summarize, the Opponents would state the following facts:

(a) ganciclovir is structurally similar (not identical) to acyclovir

(b) both acyclovir and ganciclovir are anti-viral drugs

(c) valacyclovir was developed as a successful prodrug of acyclovir and its hydrochloride salt was marketed as a successful medicine.

(d) the prior-art discloses the science and rationale behind the development of valacyclovir

(e) a prodrug of ganciclovir had to be developed

5.15. Given all these undisputable facts, it is clear that it would have been obvious to a person skilled in the art of medicinal chemistry to prepare the hydrochloride L-valine esters of ganciclovir with a more than reasonable expectation of success and that is what the inventors did, as admitted by Hans Maag (Co-inventor of the Indian Patent) in the article co-authored by him (Opponent's additional documents – dated 12.05.2009). Therefore, the claimed invention lacks an inventive step and is obvious.

Thus, the **Patent** is liable to be revoked on the above mentioned grounds.

OTHER POINTS

6. In reply, the patentee submitted that in a post grant opposition some prima facie validity is to be given to the patent. He pointed out that two of the opponents in the post grant opposition had also filed pre-grant oppositions and hence there must be some amount of insularity to the validity of the patent. In response to it was pointed that no such presumption regarding the validity of the patent is available in law. The very fact that a patent may be opposed before its grant, after its grant, could be revoked on a petition before the IPAB or in a counter claim in a suit for infringement of the patent before the High court suggests that no such presumption in law. Section 13(4) elucidates this view point and this was the interpretation of the said section of the Hon'ble Supreme Court in Bishwanath Prasad vs. Radheysham AIR 1989 SC 1444. Even though this judgment might have been rendered about two decades back, the fact remains that this was rendered in the context of Section 13(4) as it exists today. Under Article 141 of the Constitution this is the law of the land. Any argument to the contrary is not legally sustainable.

7. The reference to the format in which the patent is granted for supporting presumption of validity is irrelevant as the form cannot override the section or the Supreme Court ruling on the subject.

8. An argument was advanced by the applicant that the 18 genus of molecules identified by the opponent was flawed since the small genus of 18 was based on the prior art published on 31.5.1995 whereas the genus would have been 492 based on the prior art published on 27.6.1990. This is another irrelevant distraction tactic being employed by the Patentee. It has already been shown that the specification discloses 24 preferred compounds which is a small genus to anticipate the species claimed by the applicant. The specifications of both documents are identical; one is a published application and the other the issued patent. Without prejudice to the submission of the opponent that even a genus of 492 compounds was a small genus for the purposes of anticipating the species claimed in the present petition, it is submitted that the small genus of 24 would also flow squarely from the earlier publication by taking into account the preferred amino acids disclosed in the said publication. Hence the submission of the applicant is irrelevant and should be discarded.

9. Similarly the submission that the SPC only "covers" the product and does not anticipate, is mere play of words. The SPC is granted only if the product is shown to fall within one or more claims of a granted patent. Hence the word "covers" necessarily implies that the product for which the SPC is sought clearly falls within the ambit of one or more granted claims and by necessary implication also enabled.

10. In regard to obviousness it was submitted, there was a conflict of evidence, and hence it cannot be held that the invention was obvious to a person skilled in the art. This argument prejudges the issue. In regard to the submission that a number of countries have granted this patent and hence the US Prosecution alone should not be relied upon, it was submitted in rejoinder that the US Prosecution was relevant as the question of anticipation was raised with reference to the '329 Patent and the applicant chose not to contest the same. The applicant, is therefore, estopped from arguing the opposite before the Indian Controller.

11. In regard to Section 3(d) the applicant submitted that the term efficacy has to be given a wide meaning i.e. the plain and ordinary meaning of the term. A number of dictionary meanings of efficacy were relied upon. The applicant also pointed out that the judges are not legislators. In reply it was pointed out that while judges are not legislators they interpret the legislation and such interpretation was binding on a lower court/authority. The Division Bench of the Hon'ble High Court of Madras had interpreted the term efficacy in the context of Pharmaceutical products to be therapeutic efficacy. Hence there is no question of giving any other meaning - wide or narrow - to the said term in the context of the present opposition. The Judgment of the Hon'ble High Court of Madras and the IPAB are binding on the Hon'ble Controller. Hence all the submissions of the applicant on this account have no relevance.

12. Patentee argued that the Opponent is estopped from arguing the point that EP '329 Patent discloses mono-L-valine ester because the Opponent has stated the contrary in its other Patent Applications namely WO 2005/021549 and 1697/DEL/2005. It was pointed out by the Opponent that WO 2005/021549 states that *EP '329 Patent does not disclose the utility as well as the process for the preparation of mono-esters of ganciclovir* (Page 2; Para 1). It only states that the utility and the process or preparation of mono-ester is not disclosed and not that the monoesters themselves are not disclosed. It certainly does not mean that the Opponent has conceded that EP '329 does not disclose the mono-L-valine ester. In fact, by choosing to mention only the utility of and the process to make the monoesters, the Opponent have implicitly made a clear distinction between these two aspects and the compound itself and have implied that the monoesters themselves are disclosed. Further, Application 1697/DEL/2005 states that *EP '329 Patent discloses diester prodrugs of ganciclovir and physiologically acceptable salts thereof having improved bio-availability when administered by an oral route* (Page 2, Last Para). This statement no where seems to state that EP '329 does not disclose mono-L-valine-ester. In any case, what has been stated by the opponent in another patent application cannot operate as legal estoppel. This opposition has to be decided on the basis of the factual and legal foundation laid out in this case. Thus, this argument of Patentee is baseless and is liable to be rejected.

13. The applicant relied upon Section 115 of the Evidence Act in support of his contention that the above estoppel will operate against the Ranbaxy. It is submitted that Section 115 will not apply. Section 115 has application only when a person by his declaration had caused another person to believe the declaration to be true and makes the second person act on such declaration. In such a case, in a suit between the same two parties, the person who made the declaration will be estopped from denying the truth of that declaration. It is not the case here that based on the declaration made by the opponent herein, the patentee was made to act in any particular way. In fact the application of the patentee was much prior to the date of application of the opponent. Further, the alleged declaration made by the opponent is to the Controller of Patents who has not been led to believe or act on such declaration. Hence this argument is wholly irrelevant.

14. The advocate for the applicant stated that the affidavit of Dr. Charu cannot be given any weightage because she is an employee of the opponent. Further, it was stated that this affidavit did not contradict the affidavit of their expert Per Ljungmann. In reply it was pointed out that there was no hard and fast rule that the affidavit of an employee has to be rejected. There is no dispute that Dr. Charu is an expert. The issue is whether what has been stated by her is supported by reasoning or not. Even in the Novartis case, the IPAB nowhere held categorically that affidavits of employees cannot at all be taken in to account. The IPAB referred to certain specific paragraphs of the affidavit and stated that the averments therein cannot be said to be unbiased. In this case Dr. Charu has stated in essence that the valgan development program was built extensively on the efficacy and safety experience of Ganciclovir and that the safety profile of valganciclovir was similar to that of IV ganciclovir. There is no dispute on this factual position. Further, even with out the affidavit of Dr. Charu, the opponent had established his case under section 3(d) as clearly brought out supra. Hence, the argument of the applicant deserves to be rejected.

15. In view of the above, the Hon'ble Ld. Assistant Controller was requested to accept the opposition and revoke the petition in suit.

RELIEFS SOUGHT & PERSONAL HEARING

In light of the above submissions it is therefore humbly prayed that:

(1) the Opposition should be accepted;

(2) the Patent should be revoked; and

(3) cost should be awarded to the Opponent

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Dated: September 21, 2009

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