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The Controller of Patents  
The Patent Office  
Chennai 600 032.

*Handwritten:* COP/BPM  
22/9/09

Via Email/Courier  
September 18, 2009

Kind Attention: **Dr. S P Subramaniyan**  
**Ld. Assistant Controller of Patents & Designs**

Dear Sir,

Re: Opposition under Section 25(2) against  
Patent No. 207232  
Patent Application No. 959/MAS/1995  
Patentee: F. HOFFMAN-LA ROCHE AG  
Opponent: CIPLA LTD.  
Our Ref: PII/235/SG/cc/Y/19 10 09  
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As directed by the Ld. Controller, we submit herewith the Written Arguments in respect of the above post-grant opposition on the hearing held on September 11, 2009.

A copy of this letter (only) is marked to the Patentee for their information. A copy of the written arguments may be sent to the Patentee's attorney, if you so desire, but only after the receipt of their written arguments from the patentee. In the event, a copy of the opponent's written arguments is furnished to the applicant a copy of the patentee's written arguments should also be sent to the opponent.

The above documents may kindly be taken on record.

Yours faithfully

*Handwritten signature: Sanchita Ganguli*

Dr. Sanchita Ganguli  
Of S. Majumdar & Co  
Opponent's Agent

Encl. Written Argument (in duplicate)

c.c. DePenning and DePenning  
120 Velachery Main Road, Guindy  
Chennai – 600 032 - for information only (via email)

**BEFORE THE CONTROLLER OF PATENTS,  
CHENNAI**

Opposition to **Patent No. 207232 (959/MAS/1995)**

F.HOFFMAN-LA ROCHE AG

.....Patentee

-And-

CIPLA LTD.

.....Opponent

**WRITTEN NOTES ON ARGUMENTS OF THE OPPONENT ON THE HEARING  
HELD ON SEPTEMBER 11, 2009**

As directed by the Ld. Controller, Cipla Limited India, being the opponent in the present opposition proceedings hereby submit written notes on arguments on the hearing held on September 11, 2009.

1. The opponents started with the rebuttal for the allegation as to the locus standi of the opponent. However the patentee, at the hearing withdrew the allegation as to the locus standi of the opponent.
2. The opponents objected to the amendments made under Section 57(3) and stressed that the said amendments should have been notified for opposition. However in this case there was no advertisement of the claim amendments and hence the said amendments ought not to be allowed under Section 57(3). The patentee had volunteered not to press the amended claims since a suit is pending and contested the claims as granted. However, the opponent referred to Section 25(4), wherein the Controller can order to amend the process claims irrespective of the suit pending in the High Court.

3. The opponents relied on power point slides relating to formation of valganciclovir wherein monoester is also formed. The power point presentation described the formation of valganciclovir, its similarity in structure with valacyclovir and also the similarities with the esters of penciclovir like famciclovir and other monoesters. The print out of said power point slides are enclosed. It is evident that the structural difference with valacyclovir is that the same comprises 1OH group which is esterified with valine whereas valganciclovir has 2 OH groups which are esterified with valine. The penciclovir was shown to have 2 OH groups like ganciclovir. Its esterification occurred by formation of monoester and diester. Also hydrolysis of the diester forms monoester first, where one OH group is free and then penciclovir /deoxypenciclovir. Moreover, monoesters of penciclovir as disclosed in US 5250688 and that such monoesters existed in two enantiomeric forms and could form salts including those with hydrochloric acid was also captured in the power point presentation. Thus it is evident that formation of monoester was known in the art. Also known in the art was monoester of valine, albeit for a different but close compound.

4. The opponents drew attention of the Ld. Tribunal to the following passage of D5 as referred in the written statement of opposition:

Lines 30 to 38 of column 1 of D5 states:

*"We have now found that amino acid esters of the compounds referred to above surprisingly have advantageous bioavailability when administered by the oral route, resulting in exceptionally high levels of the parent compound in the body. This enables less drug to be administered while still providing equivalent drug levels of the parent compound in the plasma. Oral administration means patient compliance is considerably simplified."*

This clearly shows that it was known in the art to formulate ester products of ganciclovir in order to improve the bio-availability.

5. That Intravenous ganciclovir is equivalent to oral valganciclovir (powerpoint presentation) is acknowledged in Ljungman Affidavit, whereas oral ganciclovir is less

bioavailable as almost 94% is lost, thus the patentee designed a pro-drug. Accordingly it is evident that the object of the impugned patent and D5 is same i.e. to provide a better oral bio-availability of a drug for which the prodrug was prepared and that the prodrug of D5 includes valine esters of ganciclovir

As is evident from the printouts the PowerPoint presentation provided the following

disadvantages discussed and the ganciclovir per se as disclosed in the prior art and the esters of the same as disclosed in D5 was projected. Also, the formation of valganciclovir according to the present invention was projected and the bis ester of ganciclovir as disclosed in D5 was compared.

mechanism of action (valgan) such that ganciclovir is converted to the pro-drug valganciclovir which is carried to the intestine unaltered and is hydrolysed by the intestinal esterase to form ganciclovir.

prodrug mechanism as known from prior art also discussed wherein it only acts as a vehicle to carry the active drug to site of action.

## **6. Section 25(2)(b): LACK OF NOVELTY**

### **6.1 The opponent relied upon US 5043339(D5) as anticipating prior art.**

The opponent submitted that the present invention is anticipated by D5 as the compound claimed in the impugned patent is disclosed in D5 and the disclosure is enabled, i.e. a person skilled in the art on reading D5 can easily derive the allegedly claimed compound. Requirement of Law to establish anticipation.

6.2 The opponent placed the Court made laws which has diverted its course from the meaning of anticipation in the early days. Until about 1958 the law of anticipation was that a statement of prior existence of a chemical compound destroyed its novelty for subsequent claims, whether or not the skilled person would have been able to make that compound. Evidence of such position of law then can be found from the decision in **Gyogyszeripari's application** reported in 1958 RPC 51, where the Superintending Officer held as under.

*Held by the Superintending Examiner that an unrestricted claim for a chemical substance is sufficiently disclosed in a prior publication which specifies in clear terms the compound claimed and states, explicitly or implicitly, that the compound has been made.*

6.3 In later decisions the Courts took a different view and laid down the law that a prior art document can be said to be anticipatory if only a enabling disclosure is present in such document from which a skilled person would be able to derive the impugned invention by taking recourse to trial and error and routine experiments and not having to make an invention. The jurisprudence on anticipation has developed over years with the growing number of case laws. Likewise, the rudimentary concept of anticipation which found any prior art document to be anticipating with or without even investigating whether the disclosure could be worked or not, developed wherein enabling disclosure for ascertaining anticipation started to be applied.

6.4 In the case of **Asahi Kasei Kogyo KK's Application** reported in 1991 RPC at 485 to 552 where it is mentioned that an invention was not made available to the public merely by a published statement of its existence unless the method of working was so evident as to require no explanation.

6.6 The Canadian Court in the case of **Smith Kline Beecham Pharma Inc. Vs Apotex Inc.** (CA) 2002 FCA 216 (2002)(2003) 1F.C118 held that anticipation is a mixed question of fact and law. The Court has observed that "*whether the prior publication contains sufficient information to enable a person ordinary skill and knowledge in the field to understand the nature of the invention and carry it out into practical use without inventive genius but merely by mechanical skill*"

6.7 In **Smithkline Beecham PLC's (Paroxetine Methanesulphonate) Patent** reported in [2005] UKHL 59; [2006] R.P.C.10, the House of Lords -  
Held, allowing the appeal, restoring the order of the judge and finding the patent invalid for lack of novelty:

(1)Matter relied on as prior art had to disclose subject matter which, if performed, would necessarily result in an infringement of the patent. However, patent infringement did not require that the infringer should be aware that he was infringing. It followed that, whether or not it would have been apparent to anyone at the time, whenever subject matter described in the prior disclosure was capable of being performed and was such that, if performed, it must result in the patent being infringed, the disclosure condition was satisfied.

Hill v Evans (1862) 31 L.J. Ch. (N.S.) 457, HL and General Tire and Rubber Co v Firestone Tyre and Rubber Co Ltd (1972) R.P.C. 457. CA followed, Merrell Dow Pharmaceuticals Inc v H N Norton & Co Ltd (1996) R.P.C. 76, HL referred to:

(2)The infringement had to be not merely a possible or even likely consequence of performing the invention disclosed by the prior disclosure. It had to be necessarily entailed. The prior disclosure had to be construed as it would have been understood by a skilled person at the date of the disclosure and not in the light of the subsequent patent.

([23])

Merrell Dow Pharmaceuticals Inc v H N Norton & Co ltd [1996] R.P.C. 76, HL referred to T396/89 UNION CARBIDE/high tear strength polymers [1992] E.P.O.R. 312 followed.

(3)Although it was sometimes said that there were two forms of anticipatory disclosure: a disclosure of the patented invention itself and a disclosure of an invention which, if performed, would necessarily infringe the patented invention, they were both aspects of a single principle, namely that anticipation required disclosure of subject matter which, when performed, must necessarily infringe the patented invention 9[24]).

Inhale Therapeutic Systems Inc v Quadrant Healthcare Plc [2002] R.O.C. 21, Pat Ct referred to:

(4)It was the requirement that performance of an invention disclosed in the prior art must necessarily infringe the patent which distinguished novelty from obviousness. If performance of an invention disclosed by the prior art would not infringe the patent but

the prior art would make it obvious to a skilled person how he might make adaptations which resulted in an infringing invention, then the patent might be invalid for lack of inventive step but not for lack of novelty. [(25)].

(5)Enablement meant that the ordinary skilled person would have been able to perform the invention which satisfied the requirement of disclosure. This requirement applied whether the disclosure formed part of the state of the art by virtue of S. 2(2) or S. 2(3) of the Patents Act 1977. ([26]).

(6)The test of enablement of a prior disclosure for the purpose of anticipation was the same as that the test of enablement of the patent itself for the purpose of sufficiency, although there might be different in the application of this test to the facts. The authorities on s.72(1) (c) of the Patents Act 1977 were equally applicable to enablement for the purpose of ss.2(2) and 2(3) of the Act. ([27]).

T206/83 ICI/pyridine herbicides [1986] 5 E.P.O.R. 232; [1987] O.J. E.P.O. 5 and COLLABORATIVE/preprorennin [1990] E.P.O.R. 361 followed *Valensi v British Radio Corp* [1973] R.P.C. 337, *CA Mentor Corp v Hollister Inc* [1993] R.P.C. 7, *ca AND Biogen Inc v Medeva Plc* [1997] R.P.C. I.H.L referred to.

(7)It was important to keep in mind that disclosure and enablement were two different concepts, each of which had to be satisfied and each of which had its own rules. In deciding whether there had been an anticipation, there was a serious risk of confusion if the two requirements were not kept distinct. For the purpose of disclosure, the prior art had to disclose an invention which, if performed, would necessarily infringe the patent. It was not enough to say that, given the prior art, the person skilled in the art would without undue burden be able to come up with an invention which infringed the patent. But once the very subject-matter of the invention had been disclosed by the prior art and the question was whether it was enabled, the person skilled in the art was assumed to be willing to make trial and error experiments to get it to work. If, therefore, one asked whether some degree of experimentation was to be assumed, it was very important to know whether one was talking about disclosure or about enablement. ([28-31]).

Hill v Evans (1862) 31 L.J. Ch. (NS) 457, HL and Van der Lely (C.) NV v Bamfords Ltd [1963] R.P.C. 61 considered and explained.

(8) Enabling disclosure was a compendious summary of two distinct statutory requirements, which arose (as a pair) in two different statutory contexts; explicitly in s.14 (requirements for a patent application) and implicitly in determining the state of the art, whether for the purposes of anticipation or obviousness. This produced a degree of symmetry in the law and avoided divergence from the practice of the European Patent Office. ([63]).

Genentech Inc's (Human Growth Hormone) Patent [1989] R.P.C. 613, Pat Ct. Asahi Kasei Kogyo KK's Application [1991] R.P.C. 485, HL and General Tire and Rubber Co v Firestone Tyre and Rubber Co Ltd [1972] R.P.C. 457, CA referred to.

(9) The practical importance of keeping the two concepts of disclosure and enablement would vary with the factual situation. In the case of a low-tech invention, the simple disclosure of the invention would probably be enough to enable the skilled person to perform it. By contrast, in the case of a high-tech invention in the field of pharmaceutical science, the bald assertion of the existence of the invention might have to be accompanied by detailed disclosure enabling the skilled person to perform it. But in testing the adequacy of the enablement, it might be assumed that the skilled person would have to use his skill and might have to learn by his mistakes. ([64]).

(10) The role of the skilled person was different in relation to disclosure and enablement. In the case of disclosure, when the matter relied on as prior art consisted (as in the present case) of a written description meant. His common general knowledge formed the background to an exercise in construction. But once the meanings of the prior disclosure and the patent had been determined, the disclosure was either of an invention which, if performed, would infringe the patent, or it was not. The skilled person had no further part to play. For the purpose of enablement, however, the question was no longer what the skilled person would think the disclosure meant but whether he would be able to work the invention which the court had held it to disclose ([32]).

Kirin-Amgen Inc v Hoechst Marion Roussel Ltd [2005] R.P.C. 9, hl referred to.

(11) There was also a danger of confusion in a case where the subject-matter disclosed in the prior art was not the same as the claimed invention but would, if performed, necessarily infringe. To satisfy the requirement of disclosure, it had to be shown that there would necessarily be infringement of the patented invention. But the invention which had to be enabled was the one disclosed by the prior art. It made no sense to inquire as to whether the prior disclosure enabled the skilled person to perform the patented invention, since *ex hypothesi* in such a case the skilled person would not even realize that he was doing so. ([33]).

Merrell Dow Pharmaceuticals Inc v H N Horton & Co Ltd [1996] R.P.C. 76, HL referred to.

(12) There was no doubt that the prior application disclosed the existence of paroxetine methanesulfonate crystals of 98 percent purity and claimed that they could be made. Whether in fact they could be made was the question of enablement. Their existence and their advantages for pharmaceutical use were clearly disclosed in the application. On the basis of the judge's finding of monomorphism, a crystal of 98 per cent purity must necessarily have had all the characteristics of the crystals claimed in the patent, including the IR and XRD spectra. ([35]).

(13) It was immaterial that the prior disclosure attributed to paroxetine methanesulfonate crystals an IR spectrum which, on the judge's findings, was wrong. When the crystals were monomorphic, the IR spectrum was a superfluous part of the description. It may have been that the skilled person would have been puzzled or disconcerted to find that the IR spectrum of the crystals he had made following the prior disclosure turned out to be different from what he had been led to believe but he would, nevertheless have made the crystals and they would necessarily have infringed the patent. ([36])

(14) The subject-matter described crystalline paroxetine methanesulfonate and a skilled person who performed the invention of the prior disclosure, though he might, if he had

read the patent in suit, think he was not going to infringe it, would inevitably do so. ([37]).

(15) Once it had been decided that the disclosure in the prior application was crystalline paroxetine methanesulfonate and that the IR spectrum was superfluous and irrelevant, the question of enablement was whether the skilled person would have been able to make crystalline paroxetine methanesulfonate. If he did, he would necessarily have made the product claimed in the patent. There was no dispute that the disclosure enabled him to make paroxetine methanesulfonate. The issue was whether he would have been able to get it to crystallize. That was a question of fact, involving the application of standards laid down in the authorities to the evidence of the nature of the problem the assistance provided by the disclosure itself and the extent of common general knowledge. ([38]).

Mentor Corp v Hollister Inc [1993] R.P.C. 7, CA referred to.

(16) The applicant for revocation had got off to a bad start by specifying, in its main example, a solvent which had proved unsuitable for crystallization. Nevertheless, the judge had found that the skilled person would have tried some other solvent from the range mentioned in the application or forming part of his common general knowledge and would have been able to make paroxetine methanesulfonate crystals within a reasonable time. That was a finding of fact by a very experienced judge with which an appellate court should be reluctant to interfere. ([38]).

Biogen Inc v Medeva Plc [1997] R.P.C. 1, HL Applied.

(17) The decision of the Court of Appeal in the present case so intermingled the questions of disclosure and enablement that it was often difficult to ascertain which concept was under consideration. ([39]).

(18) It was not clear whether the Court of Appeal thought that the prior art did not disclose the invention or whether it did so but was not enabled. If it was the former, then the decision was wrong. If it was the latter, the Court had not offered adequate reasons

for disturbing the judge's finding of fact. The appeal would be allowed and the order of the judge restored ([50]). [55]. [65]).

6.8 The detailed findings in the body of the judgment on the basis of the headnotes were placed at the hearing and are not being reproduced for the sake of brevity.

Thus it is a requirement for anticipation that performance of an invention disclosed in prior art must necessarily infringe the invention which distinguishes novelty from obviousness. If performance of an invention disclosed by prior art would not infringe the patent but the prior art would make it obvious to a skilled person how he might make adaptation which resulted in an infringing invention, then the patent might be invalid for lack of inventive step and not for lack of novelty.

6.9 To test whether the claimed invention is anticipated it has to be therefore seen whether the cited prior art **discloses the claimed subject matter** and **whether the prior art also contains disclosure sufficient to enable the disclosed subject matter.** If we apply the above principle to the present case, on preparing a mono ester as covered by D5, it one would necessarily infringe the present application because the claimed subject matter in the impugned patent is disclosed and enabled as well in D5 as shown below for ready reference.

#### **6.10 Disclosure-**

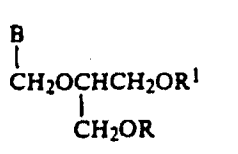
The test of disclosure is whether the compound claimed in the impugned patent is disclosed in D5.

6.11 D5 discloses a bis-valinate ester of ganciclovir in Example 5. The same document D5 at column 2, line 26-27 also discloses that the amino acid esters can be both mono and di-esters. Therefore bis-valinate ester of ganciclovir in Example 5 according to the teachings contained in D5 itself can form mono-valinate ester of ganciclovir.

6.12 Also Example 6(b) exemplifies the preparation of bis(alaninate) esters of ganciclovir containing 90% bis esters and 10% monoester. The same has been admitted by the patentee itself at page 5 of the impugned specification and page 13 of the reply statement.

The opponent submitted that D5 at column 2, line 25-26 discloses that the amino acid esters include both mono and di-esters. Thus, D5 clearly disclosed and taught amino acid mono esters as well as amino acid di-esters.

The opponent submitted that D5 discloses in line 39 at column 1, the structure of the compound claimed therein.



The opponent submitted that in total there are 3 substituents in the structure as disclosed in column 1 line 39 to 51 of D5. It is submitted that the patentee did not have to choose between cytosine and guanine as they worked on improving bioavailability of ganciclovir as admitted in the impugned specification. Thus, B always has to be guanine.

With respect to the other substituents, i.e., R and R<sup>1</sup>, it was submitted substituting any one of R or R<sup>1</sup> by a amino acid ester would yield mono amino acid esters of ganciclovir. Moreover it is clearly mentioned at column 1 lines 49 – 50 that “at least one of R and R<sup>1</sup> represents an amino acid acyl residue”. The preferred amino acids were also mentioned in line 23 at column 2 which includes valine out of the four examples. The amino acid may be in L and D form; the most preferred being L-amino acids. The preferred salts in hydrochloride salts. Further the Mitscher Affidavit at paragraph 56 mentioned that both mono and bis esters are present in D5. Accordingly there is no doubt about the disclosure of mono valine ester of ganciclovir in D5.

### 6.13 Enablement

For the purpose of enablement, the Law laid down is very clear and to establish enablement it is not required to show that the preparation of the specific compound is disclosed in D5 but there would be enablement if a skilled person using common general knowledge and carrying out trial and error experiments can arrive at the claimed product. The House of Lords in the above cited judgment held that enablement means that a person skilled in the art on going through a document would be able to perform it without undue experimentation. Before applying the test of enablement in the present case the opponents beg to place the relevant law with regard to enablement.

The EPO Board of Appeals in Case T 1120/01 – 3.3.8 was pleased to hold as under.

“6. The patent in suit provides the sequence of the DNA encoding the Fas antigen (Figures 1 and 2). It also teaches how to assay for the induction of apoptosis (Experimental Example 2). In the Board's judgment, the skilled person would be able to reproduce the claimed subject-matter (section VI supra) by routine work involving a reasonable amount of trial and errors on the basis of this information and of the common general knowledge available in 1991. Sufficiency of disclosure is acknowledged.”

The EPO Board of Appeals in Case T 223/92, the Board was convinced:

that the application provides a reliable technical teaching which placed those skilled in the art in a position to reproduce the production, cloning and expression of interferon-gamma, possibly in a time consuming and cumbersome way, but, in the given circumstances, without undue burden of experimentation and without needing inventive skill.

6.14 The opponent submitted that Example 6(b) of D5 exemplifies the preparation of 2-((2-Amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy)-1,3-propanediyl bis(L-alaninate) wherein the mono ester is formed as a 10% impurity. Isolation of such mono ester is completely within the skill of a person skilled in the art and does not require undue experimentation. Thus amino acid mono-esters are disclosed as well as enabled in D5. Example 5 of D5 discloses bis valine ester of ganciclovir. Hence the skilled worker only needed to alter at one position of the bis ester and reach the mono

ester, which is within the purview of the skilled worker given the knowledge of conventional methods of partial hydrolysis by enzymes as mentioned in specification at page 39.

**The opponent further submitted that enablement is common general knowledge in addition to the disclosure in the specification.** Accordingly as there is disclosure of bis valine ester of ganciclovir and other monoester of ganciclovir of D5 and given the isolation of monovaline ester ganciclovir is admittedly by conventional method (which is part of common general knowledge of a person skilled in the art), the attention of the Ld Tribunal was drawn to: -

**6.15 Mitscher Affidavit (paragraph 56) where he has stated that both mono and di esters of the compound are included but '339 does not isolate or test the monoester. Isolation of the monoester from a mixture of bis and mono ester can be performed by conventional techniques as evident from the Patentee's own admission at page 38 of impugned specification wherein it is mentioned that "the compounds of this invention may also be prepared from 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediyl bis(L-valinate) which is described in EP 0375329 (D6). The conversion to 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-3-hydroxy-1-propanyl-L-valinate is effected by partial hydrolysis (Step e) of one L-valine ester group under controlled conditions which result in the preferential cleavage of only one amino acid acyl residue. The monoester can be separated from the bis ester by preparative chromatography under weak acidic....."**

However, as mentioned above, since monoesters are formed while formation of bis ester and formation of bis valine ester of ganciclovir is exemplified in D5 the formation of monoester is already taught and its isolation being admittedly by conventional method is within the purview of the person skilled in the art and hence the working/isolation of self evident from D5.

**6.16** In this regard the attention of the Ld Tribunal was drawn to Pg 11 of Expert affidavit of Dr. Rao – "With respect to paragraphs 60 to 63 wherein Dr. Stella has pointed out that the '339 patent and the EP 329 patent teach only bis-esters and do not

provide isolation of monoesters or any demonstration as to the degree of their oral bioavailability, I say that the process described in EP'329 is applicable to the preparation of monoesters as well by virtue of the fact that a monoester may be prepared by a similar technique with a mere modification of the substrate: reagent ratio. Furthermore I say that small amount of monoesters do form in the process for preparation of the diesters and vice-versa. Thus the argument of Dr. Stella that isolation of monoesters is not described is wholly irrelevant and a mere acknowledgement of the fact that monoesters inherently form in any synthetic process leading to the formation of diesters. As regards the isolation of the monoester, I say that the same may be separated by using conventional physical methods of separation and do not require explicit teaching in any document since the same is available in standard literature. I further note that Example 6 (b) on page 9 of the EP '329 patent clearly indicates that the product of the reaction i.e. the bis(alaninate) ester is a mixture of the O-monoesterified and O,O-diesterified products in the ratio of 1:9 which proves beyond doubt that the monoester formation inherently occurs during the synthesis of the di-ester."

6.17 Thus it is evident that given the disclosure of D5 it is only matter of routine experimentation by conventional method to reach the impugned patent, which ought to be part of common general knowledge available to a person skilled in the art. The attention of the Ld. Tribunal was drawn to the **Exhibit Q of Stella Affidavit at page 245, which discloses a flow chart showing the enzymatic hydrolysis from a diester ganciclovir to its mono-ester to finally yield ganciclovir.** To further reinforce that formation of monoester from diester could be done without undue routine experimentation the attention of Ld. Tribunal was drawn to Hodge et al 1989(submitted by the opponent with their letter on or about May , 2009) which shows various monoester of penciclovir being formed specifically as described in Table1 and the scheme in Figure 5, from which the monoester of ganciclovir could easily be prepared by routine experimentation.

6.19 The Expert's (Dr Rao's) comments and the other documents referred, other than the anticipating prior art (D5), all go to show that the techniques of hydrolysis, isolation

and other methods of purification form part of common general knowledge of a person skilled in the art, which enables a person to work the disclosure of D5.

6.20 It was further pointed out that HCl salt is FDA approved and most used and is also disclosed in D5.

6.21 No evidence has been adduced by patentee to show that on following the teachings of D5, one would face hurdles and that the present invention has overcome such hurdles by way of the novel process used in the present invention. Accordingly it was pointed out that the disclosure of D5 is enabled enough for a person skilled in the art to carry out the same by routine trial and error. Further, no evidence given by patentee in support of the fact that D5 does not have an enabling disclosure whereby the isolation of mono from bis was difficult and they had to carry out the present invention. On the contrary the specification at page 37 itself mentions isolation by conventional methods.

6.22 The Patents Court in the case of Toyama Chemical Co. Ltd. Application reported in [1990] R.P.C. 555, allowed further adjournment wherein the applicants could submit further evidence to prove that the anticipatory prior art was not enabled.

“(6) The applicants must either submit amendments to overcome the novelty objection under Section 2(3), or they must challenge the claimed priority date of the cited document or otherwise challenge the validity of the novelty objection. Evidence in support of such challenge was not required at this stage.

The applicants appealed to the Patents Court, and subsequently filed at the Patent Office experimental evidence to show the lack of enabling disclosure to support the priority claim in the cited document. The Office refused to consider this evidence. It was admitted by the court, which then adjourned the hearing so that argument on the law relating to enabling disclosure could be heard. In the meantime that point of law was decided in Genentech Inc.’s (Human Growth Hormone) Patent, [1989] R.P.C. 613, but the Office criticized the evidence which the applicants had already filed. The applicants then applied to the court for a further adjournment to put in more evidence.”

The opponent would briefly discuss the facts of the aforecited case. In said case, the application of Toyama was objected since it was found to be anticipated by a prior art document. The patentee must either submit amendments to overcome the novelty objection, or they must challenge the claimed priority date of the cited document or provide evidence in support of such lack of enabling disclosure. Applicants had no choice but to traverse on the ground that the disclosure of the prior art was not enabling and hence anticipation cannot be established. To support such traversal, the applicant provided experimental data to show that the disclosure of the anticipating document could not be performed. Since, the applicants wanted to do further experiments to adjournment was sought. **In the present case too, the patentee cannot incorporate disclosures to leave out the compounds as disclosed in D5 which would amount to withdrawing its product claims, thus the patentee have no choice but to provide evidence by way of some experimental data which would go to show that following the process of e.g. 6(b) of D5, and then isolating the monoester does not involve any undue experimentation.**

**Though the case mentions that to meet the objection of anticipation, patentee have the option of deciding through arguments or evidence or a combination of both, the opponent submitted in the present case, the allegations on anticipation are strong and the patentee ought to have submitted some data to support its contention that the disclosure of D5 is not enabling. The patentee at page 13 of the reply statement has very clearly submitted that the disclosure in D5 does not amount to enabling disclosure. The opponent submitted that making such bald statement without any supporting data cannot overcome an allegation of lack of novelty.**

6.23 Thus the definition of enablement quite clearly flows from the above cited decisions, a disclosure meets the requirement of sufficiency when a skilled person would be able to carry out/reproduce claimed subject matter by routine work based on the information and common general knowledge available.

**6.24 Reverse test of infringement is the final test for determination of anticipation.** Paragraph 3 of the House of Lords judgment cited hereinabove, paragraph 3 of the headnotes of said judgment reads as under.

“Although it was sometimes said that there were two forms of anticipatory disclosure: a disclosure of the patented invention itself and a disclosure of an invention which, if performed, would necessarily infringe the patented invention, they were both aspects of a single principle, namely that anticipation required disclosure of subject matter which, when performed, must necessarily infringe the patented invention 9[24]).”

If one prepares L-valine monoester of ganciclovir in accordance with the teachings in D5 along with the common general knowledge available to him, it would infringe the patent under opposition. Thus, amino acid mono esters are disclosed in D5 and such disclosure is enabling. Thus, the reverse test of infringement is fully satisfied and the impugned patent is anticipated.

**6.25 Following the findings of the Courts and all other authorities placed before the Ld. Controller, the Ld. Controller has to arrive at the finding whether the making of the monoester of the known compound was an unreasonably difficult exercise having regard to what is taught in D5, especially the portions of D5 indicated above and having regard to common general knowledge.**

6.26 The opponent referred to paragraph 10 of its written statement of opposition wherein the wherein the prosecution of the US counterpart of the present application has been dealt with briefly. The claims filed with regard to the product initially was drawn to valganciclovir however final claim amendments go to show that the claims are directed to valganciclovir in crystalline form, which reasserts the submissions of the opponent as to the disclosure of L-monovaline ester of ganciclovir in D5.

**6.27 The patentee in its reply statement at pages 13 and 14 elaborately discuss**

D5, in distinguishing the present invention from the that of D5 submits that the prior art does not teach the preparation and the usefulness of L-monovaline ester of ganciclovir and then further submits the bioavailability improvement data over bis-valinate esters. The opponent submits that it never contended that the preparation of mono-ester was disclosed per se in D5, but all it submitted was that for a skilled person enablement of the disclosure as to the formation of mono-esters were a part of his common general knowledge at the priority date of the impugned patent. Moreover, utility does not render a molecule novel under the law as would be evident from the US judgments cited hereinbelow.

In the case of *In Re Ronald D Schoenwald and Charles F Barfknecht*, 964 F.2d 1122, the US Federal Circuit held as under.

*5. Paramount among the patentability requirements is that that which is sought to be patented must be new. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 780, 227 USPQ 773, 777 (Fed.Cir.1985). Simply put, the compound claimed by Schoenwald is not new. Under section 102(b), one is not entitled to a patent on a compound if it "was patented or described in a printed publication in this or a foreign country ... more than one year prior to the date of the application for patent in the United States." Phrased differently, section 102(b) prohibits the patenting of a compound if it is anticipated by a prior printed publication. While the mere naming of a compound may not be enough for anticipation, a reference which describes and enables has been held sufficient. In re Wiggins, 488 F.2d 538, 543, 179 USPQ 421, 425 (CCPA 1973), In re Brown, 329 F.2d 1006, 1011, 141 USPQ 245, 249 (CCPA 1964). But Schoenwald would go further: he argues that an anticipatory reference must also disclose a use.*

10. In essence, appellant is contending that a double standard should not be applied in determining the adequacy of a disclosure to anticipate under § 102, on the one hand, and to support the patentability of a claim under § 112 on the other. He feels that a disclosure adequate for the one purpose is necessarily adequate for the other but, unhappily for him, this is not so. As we shall develop, a disclosure lacking a teaching of how to use a fully disclosed compound for a specific, substantial utility or of how to use for such purpose a compound produced by a fully disclosed process is, under the present state of the law,

entirely adequate to anticipate a claim to either the product or the process and, at the same time, entirely inadequate to support the allowance of such a claim.

11. Id. at 1405, 161 USPQ at 785 (footnotes omitted). This discussion was not dictum because by adhering to the rule that utility need not be disclosed to anticipate a claim to a compound, but must be for enablement, the rejection of applicant's claims was affirmed. To the same effect were In re Samour, 571 F.2d 559, 563, 197 USPQ 1, 5 (CCPA 1978) ("Appellant's further argument that 'some practical utility' for [the invention] must be disclosed in the prior art before [the prior art reference] can serve as a statutory bar ... is also not persuasive"), and In re Donohue, 632 F.2d 123, 126 n. 6, 207 USPQ 196, 199 n. 6 (CCPA 1980) ("proof of utility is not a prerequisite to availability of a prior art reference under 35 U.S.C. § 102(b)").

13. discovery of an unobvious property and use does not overcome the statutory restraint of section 102 when the claimed composition is known. While Spada's position is that his polymers are not anticipated by the polymers of Smith because their properties are different, Spada was reasonably required to show that his polymer compositions are different from those described by Smith. This burden was not met by simply including the assertedly different properties in the claims. When the claimed compositions are not novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior art.

**In the present case too, the patentee submits in its reply that the usefulness of the claimed compound is not mentioned in prior art (D5), which distinguishes it from D5 vis-à-vis novelty. In the afore-cited case too, the applicant contended that that the anticipatory prior art must disclose a use. The court held that no utility requirement is necessary for a reference to be anticipatory. Thus, in the present case the enabling disclosure of the L-monovaline ester of ganciclovir is enough to prove anticipation, the utility of the same need not be specified in the anticipatory document, i.e., D5.**

**In the case of Impax Laboratories Inc v. Aventis Pharmaceuticals Inc, 468 F3d 1366, the US Federal Circuit held as under.**

71. In order to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed.Cir.2003); *Helifix, Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1346 (Fed.Cir.2000); *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed.Cir.1986). Prior art is not enabling so as to be anticipating if it does not enable a person of ordinary skill in the art to carry out the invention. See *Elan Pharms., Inc. v. Mayo Found.*, 346 F.3d 1051, 1057 (Fed.Cir.2003) (remanding the case to the district court for a determination of whether the prior art reference enabled persons of ordinary skill to make the invention without undue experimentation); *In re Donohue*, 766 F.2d 531, 533 (Fed.Cir.1985) ("[P]rior art . . . must sufficiently describe the claimed invention to have placed the public in possession of it. Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention.") (citation omitted).

72. **The enablement requirement for prior art to anticipate under section 102 does not require utility, unlike the enablement requirement for patents under section 112.<sup>2</sup>** (.....) We reversed the Board's determination that the prior art was not enabling and remanded the case for consideration of anticipation, **holding that proof of efficacy is not required for a prior art reference to be enabling under section 102.** *Id.*; see also *Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 424 F.3d 1347, 1355 (Fed.Cir.2005) ("The standard for enablement of a prior art reference for purposes of anticipation under section 102 differs from the enablement standard under 35 U.S.C. § 112. . . . While section 112 'provides that the specification must enable one skilled in the art to "use" the invention,' . . . 'section 102 makes no such requirement as to an anticipatory disclosure,' . . . **Significantly, we have stated that 'anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art.'**" (citations omitted)); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1378 (Fed.Cir.2001) (holding that prior art that suggested a drug was ineffective nevertheless

anticipated a patent on that drug); *Celeritas Techs. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed.Cir.1998) ("A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis.").

73. "Whether a prior art reference is enabling is a question of law based upon underlying factual findings." *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed.Cir.2002). In *Amgen*, we stated that, when, as here, **an accused infringer asserts that either claimed or unclaimed material in a prior art patent anticipates patent claims asserted against it, the infringer is entitled to a presumption that the allegedly anticipating material is enabled. 314 F.3d at 1355 ("[A] court cannot ignore an asserted prior art patent in evaluating a defense of invalidity for anticipation, just because the accused infringer has not proven it enabled.").** However, "[i]f a patentee presents evidence of nonenablement that a court finds persuasive, the trial court must then exclude the particular prior art patent in any anticipation inquiry, for then the presumption has been overcome." *Id.* In this case, the issue is whether the prior art enables the treatment of a specific disease with a specific compound.

E.

74. (.....) However, as we recognized in *Rasmusson*, proof of efficacy is not required for a prior art reference to be enabling for purposes of anticipation. 413 F.3d at 1326. That is, a section 102 prior art reference does not have to be "effective" to be enabling and thus anticipating. *Id.* Under *Rasmusson*, the effectiveness of the prior art is not relevant. *Id.* Rather, the proper issue is whether the '940 patent is enabling in the sense that it describes the claimed invention sufficiently to enable a person of ordinary skill in the art to carry out the invention. As seen above, however, the district court focused only on the former question. Thus, we remand to allow the district court to make the proper factual determinations and then reach its own legal conclusion as to whether the '940 patent is enabled.

75. (.....) Here, with the large number of compounds included in formula I and no specific identification of riluzole by the '624 application, the '624 application does

not disclose riluzole, and therefore, cannot enable treatment of ALS with riluzole. The '624 application cannot anticipate any of claims 1-5 of the '814 patent.

76(.....) On remand, the district court should determine whether the '940 patent is enabling, using the proper legal standard. That has not yet been done because, as seen, the district court stopped its analysis after concluding that the '940 patent did not disclose that the compounds of formula I were effective in treating ALS. What the district court must determine on remand is whether the disclosure of formula I in the '940 patent enables a person of ordinary skill in the art to carry out the invention claimed in claims 1-5 of the '814 patent. See *Elan Pharms.*, 346 F.3d at 1057. Specifically, the district court must determine whether the '940 patent enables a person of ordinary skill in the art to treat ALS with riluzole. **Effectiveness in treating ALS does not have to be established.** See *Rasmusson*, 413 F.3d at 1325-26. If the district court determines that what is disclosed in formula I of the '940 patent is enabling in that a person of ordinary skill in the art can carry out the invention, then it will be for the district court to determine whether that disclosure anticipates claims 1-5 of the '814 patent. If, however, the district court determines that what is disclosed in formula I of the '940 patent is not enabling in that a person of ordinary skill in the art could not carry out the invention, then the district court should again hold that claims 1-5 of the '814 patent are not anticipated by the disclosure of the '940 patent and that therefore claims 1-5 are not invalid.

In the above case, the bolded portions lay down the legal principles applicable as to enablement for the purpose of anticipation. The district Court in the above matter found that there was no disclosure of the compound in the anticipatory prior art and accordingly did not go into the test of enabling disclosure. However, on appeal to the Appeal Court, the matter was remanded to the district Court and the proper determination of enabling disclosure to be followed by the District Court was laid down by the Appeals Court. Hereto, the patentee's contended that the usefulness/effectiveness of the patented compound was not found in the anticipatory document and the Appeals Court held that effectiveness does not have to be established for determining anticipation. Herein, the patentee submits that the

**utility of the L-monovaline ester of ganciclovir is not found in D5. The opponent states that following the principle laid down by these Courts, it is settled law that utility is not a requirement for determination of anticipation. Hence, the disclosure of the compound and the common general knowledge which enables a skilled person to prepare claimed compound clearly anticipates the claims of the impugned Patent.**

Thus the claims of the impugned patent ought to be revoked under Section 25(2)(b).

## **7. Section(25)(2)(e): OBVIOUSNESS**

**7.1 L- monovaline ester of ganciclovir is nothing but a prodrug of ganciclovir as admitted by the patentee itself at page 10 of the impugned specification. Prodrugs function as inactive vehicles and carries the drug to the site of action by way of which it makes the active molecule more bioavailable at said site. Such mechanism is also well known in the art and the same is substantiated by the documents relied upon at the hearing by the opponent.**

**7.2 The need which is allegedly met by the alleged invention was to develop an oral dosage form with improved bioavailability for the treatment of CMV infection. The patentee met the need by formulating a prodrug of ganciclovir, specifically an L-monovaline ester of ganciclovir which had improved oral absorption and low toxicity, though there is no data on low toxicity has been exemplified in the impugned specification.**

**7.3 The opponent submitted that such increase in oral absorption is completely expected in view of the teachings available on prodrug as well as on prodrugs of similar antiviral drugs used for CMV infection.**

**7.4 The opponent referred to the power point presentation which was presented at the hearing, where it was submitted that D11 (Beauchamp et al 1992) clearly taught valacyclovir, the valine monoester of acyclovir was found to have the best bioavailability and Exhibit Q of the Stella affidavit, at the very last sentence at page 243(internal page) clearly mentions that finding of the workability of esters of acyclovir inspired the authors of the Exhibit Q to try similar esters of ganciclovir.**

7.5 The opponent thus submit that the finding of the improved bioavailability of the valine monoester of ganciclovir clearly motivated/inspired the present inventors to try amino acid monoesters of ganciclovir for the same purpose.

7.6 Regarding the **lowering of toxicity, the opponent relied upon the Label information of Valcyte at pages 15, 18 and 22 clearly teach that adverse events associated with valganciclovir is same as those with ganciclovir.** The opponent thus submits that the toxicity associated with the L-monovaline ester of ganciclovir as claimed in the impugned patent is not reduced.

7.7 The opponent at the hearing due to could not extensively rely upon every prior art document submitted by it, but focused on some of the more significant ones. The prior art documents which could not be referred at the individually shall not be treated as withdrawn.

7.8 The teachings of the prior art documents along with the page and line numbers relied upon at the hearing has been tabulated for the sake of convenience.

Annexure 1: Robert E. Notari; "Prodrug Design"	<p>The general concept of prodrug as provided at page 25 of said Annexure I indicates that though there is no strict universal definition "<i>a prodrug is an inactive compound formed by intentionally linking a drug to an inert chemical by a covalent bond which may be broken (by any mechanism) to yield drug itself in vivo</i>"; At page 27 para 1.3- under the sub-heading prodrug candidates and conversions it is mentioned that "<i>Sinkula and Yalkowsky 1975 have summarized the possible enzyme-reversible product linkages as – aliphatic esters, carbonate esters, hemiesters, phosphate esters, sulfate esters, amides, azolinkages, carbamates.....by far the most widely used prodrug linkage is that of an ester wherein the original drug provides either the carboxylic acid or the hydroxylic group. Add to this the phosphonates, carbonates and hemiesters and one had accounted for the large majority of prodrugs.</i>"</p> <p>At page 47 under pharmacokinetic analysis it is mentioned that 'most reported prodrugs appear to have been intended to increase</p>
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	<p>oral absorption, prolonged shelf life of injectables, decrease pain or injection, improved test or produce i.m depot injections'. At page 48 it is mentioned that <i>'ideally these prodrugs would have rapid and complete absorption characteristics with immediate conversion to drug in the blood'</i>. At page 49 it is mentioned that <i>'an early example of a nucleoside prodrug for improved oral absorption appeared in 1969'</i>. Accordingly the opponent states that the prodrugs are substances which includes esters and hemiesters of the drugs such that they could be clipped easily and release the drug in the body and moreover prodrugs for improved oral absorption and specifically nucleoside prodrugs for such purposes were known as early as 1969.</p> <p>Thus designing a prodrug for improving bioavailability does not involve any inventive merit when such prodrugs were already known.</p>
Exhibit 7 (of Mitscher Affidavit): Harnden et al	<p>This article discusses prodrugs of 9-[4-hydroxy-3-(hydroxymethyl) but-1-yl] guanine (BRL 39123) which has improved bioavailability. The abstract teaches that both di-ester and monoester prodrugs of BRL 39123 was well absorbed and efficiently converted to BRL 39123 after oral absorption. <b>The attention of the Ld Tribunal was drawn to page 1739 under the subheading Chemistry, where preparation of the prodrugs is described. It is clearly mentioned in this portion that diacetelated compounds are dacetelated to yield the free base while stopping the reaction partway yielded the monoester.</b> Thus clearly it teaches that stopping reaction partway can lead to formation of monoester. It is further taught that starting from the free base selective protection and deprotection and selective O acylation leads to formation of monoesters. <b>Schemes I and II at page 1739 of Annexure 2 elucidate the formation of monoesters by the reduction of bis-esters and from the free base(deoxy penciclovir) by selective acylation. Thus production</b></p>

	<p>of monoester both from the bisester as well as the free base is taught in Annexure II albeit for a different but structurally close nucleoside analogue namely penciclovir. Compounds 15, 17 and 21,22 are monoesters and compound 19 has hydroxy and amino protecting groups from which the monoesters 21 and 22 are formed by deprotection. Thus, the process of preparation of monoesters by reducing the bis-esters.</p> <p>At page 1740, it further teaches that ester derivatives 14-17, 21 and 22 out of which 15 and 17 and 21 and 22 are monoesters and showed efficient absorption.</p> <p>It further teaches at page 1741 under the summary clearly teaches that derivatives of 5 including 15 and 17 are well absorbed and efficiently converted to BRL 39123 upon administration.</p> <p>Though diesters were selected for further studies, it is submitted that it does not amount to teaching away as the document does not explicitly mention any disadvantages associated with the use of monoesters. It only says it is better absorbed, which does not mean that the mono esters are useless.</p> <p>Thus this document clearly teaches formation of monoesters using protection deprotection and selective acylation (esterification) which clearly motivates the impugned patent where similar process is followed to arrive at the monoester prodrug which improves the bioavailability over the parent compound. As the bis valine ester of valganciclovir was already tried and tested at the priority date of the impugned patent, the patentee merely had to carry out routine experiments to check whether the mono valine esters had similar or more bioavailability and finding that it has better bioavailability than the bis ester is only by trial and error and no inventive faculty can be accrued to the same.</p>
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Exhibit 9 Hodge et al, 1989 (filed with letter in May, 2009)	<p>The Abstract mentions that the limited oral availability of the drug penciclovir lead to the development of prodrug famciclovir which shows better bioavailabiliry. <b>Table 1 at page 1767 shows the conversion of bis ester to mono ester both of penciclovir and deoxypenciclovir. Further reference was made to Fig5 at page 1772 which shows the scheme of conversion of famciclovir to the mono ester and then finally to penciclovir.</b> Thus the formation of monoester from the bis ester of penciclovir is known and there cannot be any inventive faculty in finding the same for ganciclovir.</p>
Exhibit 8/Exhibit K annexed to Mitscher Affidavit and Stella Affidavit	<p>The first paragraph at page 181 teaches the preparation of mono-O-acyl derivatives of DHPG also exemplified in Scheme III therein below. The process as exemplified requires the selective protection of one of the two primary hydroxyl functions in DHPG and hence the document teaches formation of mono esters by selective protection and deprotection as in the impugned patent..</p> <p>Under the discussion section at page 182, it teaches that mono acyl derivative, dicarbamate and dicarbonate derivative exhibited reduced activity.</p> <p><b>Thus, there is no thumb rule that diesters would always have improved activity while mono esters would have reduced activity. This document substantiates the fact that such activity varies and the same can be tested and tried for mono or diesters.</b></p>
Brewster et al	Enhanced delivery of ganciclovir to the brain was observed in this study. The ganciclovir used was in monoester form and the results

	<p>go to show that the drug was more bioavailable in the brain than when delivered in oral ganciclovir.</p> <p>Thus, monoesters has been used in prior art wherein the bioavailability of the compound showed improvement. Thus, the patentee was aware of such knowledge and merely tested the monoester to verify such knowledge. Thus, the patentee had a reasonable expectation of success that monoesters would provide improved bioavailability.</p>
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7.9 The opponent submitted that the impugned patent claims lack inventive step and thus obvious to a person skilled in the art.

7.10 It is evident from the above referred documents that prodrugs are known to have increased bioavailability and are designed for the exact same purpose. Prodrug by itself is inactive and metabolizes at the site of action to release the active metabolite. In the present case, when the inventors wanted an antiviral agent with improved bioavailability, they took ganciclovir which was the then best drug for treatment of CMV infection and and tested a monoester prodrug of the same as the mono and bis-ester were already known..

**7.11 The bioavailability of the oral monovaline ester of ganciclovir is same as ganciclovir when administered intravenously as admitted by its Expert Dr. Ljungman .** Thus, the alleged invention is more of a patient compliance therapy than bringing about some surprising and unexpected therapeutic benefits as the antiviral activity of the molecule remains the same. **(Notari et al) clearly teaches that pro-drugs are prepared to deliver the active metabolite at the site of action without any loss in activity.** Also nucleotide or nucleotide residues have negative charges and these pro-drugs mask such charge and delivers to the active to the said site. Thus, the concept behind designing such prodrugs was amply clear at the priority date of the impugned patent. And a person looking for means to improve bioavailability, especially by preparing prodrugs ought to be aware of the cited references, Annexure 1 in particular.

7.12 The opponent states that **Notari et al read with Harnden et al completely motivates a person skilled in the art to try monovaline esters of ganciclovir as**

monoesters were found to have improved activity. The opponent further states that from it is clear on reading Annexure 3 that esters with free 'OH' groups are viable. Thus, leaving an 'OH' group free would not lead to any toxicity which would demotivate a skilled person from preparing monoesters. Moreover the Label information of Valcyte itself mentions that the toxicity of the prodrug is the same as that of the drug itself. Annexure 4 and 5 teach such ester derivatives may exist in enantiomeric forms. Annexure 5 in particular mentions that when one of the acetyl ester groups is hydrolyzed it resulting monoesters are chiral compounds. Thus, the product claim as claimed in claim 1 of the impugned patent is entirely obvious in light of the above referred citations and the others cited alongwith the representation.

7.13 The opponent submitted that in Paragraph 34 of reply statement- patentee misinterpreted paragraph's 7.5 and 7.6 of the written statement of opposition. In paragraph 34 of the reply, patentee discusses with respect to D5 and formation of prodrug of ganciclovir, which is not disclosed in the said document and only the compound ganciclovir is disclosed therein. **The opponent submitted that the instance of ganciclovir as disclosed in D5 was placed to show that ganciclovir was a known compound and that in combination with teachings of D11 demonstrating valine ester of acyclovir to be the most bio-available amino acid ester a person skilled in the art could reach the present invention without inventive merit.** Thus there is clear motivation to form valine ester prodrug in order to improve bioavailability of a nucleotide analogue and reach the mono valyl ester of ganciclovir.

7.14 It was pointed out that in D11 the solution for improved bio-availability with respect to acyclovir was formation of the valine ester of the same namely valacyclovir, so there was clear motivation remained to try mono-valine ester of ganciclovir. This is further evident from Exhibit Q of Stella – pg. 243 last paragraph on left hand column which reads as under. "We have recently shown that N-substituted 3- or 4-(aminomethyl) benzoate esters of acyclovir which structurally closely resembles ganciclovir, are promising pro-drug derivatives, in particular for parenteral or ocular administration. The esters combine a high solubility and stability in weakly acidic solutions with a high susceptibility to undergo enzymatic hydrolysis in plasma. This finding inspired us to examine the behaviour of similar ester of ganciclovir." However on

the one hand the patentee states in the reply statement that D11 is not a relevant prior art as it does not contain indication or disclosure or guidance towards prodrug of ganciclovir while the quoted portion above from Exhibit Q of Stella Affidavit clearly mentions that the working of ester of acyclovir provided impetus for looking into the activity of similar ester of ganciclovir. Accordingly since ganciclovir was admittedly known to be the best antiviral against CMV with requirement of improved bioavailability and D11 teaching monovaline ester of acyclovir providing improvement of bioavailability over acyclovir it was obvious to try the said monovaline ester of ganciclovir to improve its bio-availability with reasonable expectation of success.

**7.15 The opponent also submitted that when a compound is prima facie obvious, the patentee should provide some evidence in form of comparative data to show that the claimed compound has unexpected properties vis-à-vis the teachings of prior art. The experimental data submitted by the Patentee in the specification showing improved bioavailability over the bisester, does not show the surprising effect since the document by Martin et al which has been submitted by the patentee along with the Reply statement as well as with Affidavits of Dr Stella and Dr Mitscher shows that both mono and bis esters of ganciclovir can have reduced activity. Therefore there is no hard and fast rule that the mono ester will always have reduced activity and the bis-ester will always have more activity. It rather shows that the mono esters are worth trying since in case it has better activity and that is what the patentee has done tried the options available.**

**7.16 Though the patentee raised objection that the process claims have not been pleaded in the Written Statement of opposition, some portions mentioned therein was brought to the notice of the Ld Tribunal. The opponent submitted that the process claim as claimed in claim 10 is unclear as it mentions several alternative processes. It was also pointed out that step 10(d) which relates to the step of condensation, does not even have mention valine among the substituents of Y<sup>1</sup> and Y<sup>2</sup> in the formula. The patentee is trying to formulate ester of valine without even having valine in the components. Such claims are completely infructuous and ought to be rejected. The process involving protection and deprotection of the amino and the hydroxy group are, as mentioned above taught in Exhibit 7 of Mitscher Affidavit and the same is**

not repeated for sake of brevity and selective acylation (esterification). Colla et al submitted with the written statement of opposition also teaches protection and deprotection of hydroxy and amino group in formation of the mono ester of acyclovir. Thus the use of protection and deprotection was known in the art in the formation of esters before the date of the impugned patent.

7.16 The opponent's relied upon the following decisions to support its submissions on the ground of inventive step:

**The U.S. Supreme Court in the case of Atlantic Works v. Brady 107 U.S.192 (1883), held as under.**

The design of the patent laws is to reward those who make some substantial discovery or invention which adds to our knowledge and makes a step in advance in the useful arts. Such inventors are worthy of all favor. It was never the object of those laws to grant a monopoly for every trifling device, every shadow of a shade of an idea, which would naturally and spontaneously occur to any skilled mechanic or operator in the ordinary progress of manufactures. Such an indiscriminate creation of exclusive privileges tends rather to obstruct than to stimulate invention. It creates a class of speculative schemers who make it their business to watch the advancing wave of improvement and gather its foam in the form of patented monopolies which enable them to lay a heavy tax upon the industry of the country without contributing anything to the real advancement of the art. It embarrasses the honest pursuit of business with fears and apprehensions of concealed liens and unknown liabilities to law suits and vexatious accountings for profits made in good faith.

In the present case, the opponent submitted that the present invention as claimed by the impugned patent is completely obvious in view of the other monoesters of similar antiviral drugs that already exists, valacyclovir in particular. Valacyclovir is also a monovaline ester of acyclovir which was found to have improved bioavailability than acyclovir, in light of such teaching a person of ordinary skill in the art would be motivated to try monovaline ester of ganciclovir, specially when the Exhibit Q of Stella

clearly mentions that esters of acyclovir inspired to develop esters of ganciclovir. Herein the present inventors possessing knowledge of the entire gamut of prior art, were inspired/lead to try the L-monovaline ester of ganciclovir and found the compound to possess superior bioavailability, which cannot be regarded as inventive but only obvious to try.

**The Federal Circuit in the case of Pfizer, Inc. v. Apotex, Inc. held as under.**

*“Reasonable Expectation of Success - As noted above, the district court found that the skilled artisan would have had no expectation of success in making a besylate salt of amlodipine because there was no reliable way to predict the influence of a particular salt species on the active part of the compound. We cannot reject the district court’s finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be. The problem with the district court’s ultimate conclusion of non-obviousness based on that factual finding, however, is that case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.*

*A. There was an expectation, but that wasn’t guaranteed.*

*But, once again, only a reasonable expectation of success, not a guarantee, is needed.*

*First, this is not the case where there are “numerous parameters” to try. Rather, the only parameter to be varied is the anion with which to make the amlodipine acid addition salt. Although we recognize some degree of unpredictability of salt formation, see, e.g., Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1379 (Fed. Cir. 2006), the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious. This is especially true here, where (1) as noted above, the skilled artisan had a reasonable (although not guaranteed) expectation that amlodipine besylate would form; (2) Pfizer conceded in prior litigation that the type of salt had no effect on the therapeutic effect of the active ingredient, amlodipine, and was practically interchangeable, Pfizer v. Dr. Reddy’s Labs., 359 F.3d at 1365-66; and (3) numerous other publications (described above) clearly directed the skilled artisan to a pharmaceutically-acceptable acid addition salt made from benzene sulphonate, including, significantly, the Carabateas patent which taught the besylate acid addition salt form of another dihydropyridine pharmaceutical compound.*

*Second, this is not the case where the prior art teaches merely to pursue a “general approach that seemed to be a promising field of experimentation” or “gave only general guidance as to the particular form of the claimed invention or how to achieve it.”*

*The experimentation needed, then, to arrive at the subject matter claimed in the ’303 patent was “nothing more than routine” application of a well-known problem-solving strategy. Merck, 874 F.2d at 809, and we conclude, “the work of a skilled [artisan], not of an inventor.” DyStar, 464 F.3d at 1371; see also In re Luck.*

*Thus, while patentability of an invention is not negated by the manner in which it was made, “the converse is equally true: patentability is not imparted where ‘the prior art*

would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success.” Merck, 874 F.2d at 809 (quoting *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988)). For these reasons, we hold that Apotex introduced clear and convincing evidence that a skilled artisan would have had a reasonable expectation of success with the besylate salt form of amlodipine at the time the invention was made. Accordingly, we agree with the district court that a prima facie case of obviousness was established with regard to the claims of the '303 patent, albeit for different reasons.

Unrebutted testimony from Apotex's expert evidences that, given the range of 53 anions disclosed by Berge, one skilled in the art would expect those anions to provide salts having a range of properties, some of which would be superior, and some of which would be inferior, to amlodipine maleate. Pfizer has simply failed to prove that the results are unexpected. Boesch, 617 F.2d at 278.

The district court wrongly relied on the fact that the “besylate salt works” because considerable evidence shows that amlodipine maleate also worked for its intended purpose and even did so in human clinical trials, even though somewhat inferior in ease of tableting and projected shelf-life. At most, then, Pfizer engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts to ease its commercial manufacturing and marketing of the tablet form of the therapeutic amlodipine.

In re Swain, 156 F.2d 246, 247-48 (C.C.P.A. 1946) (“In the absence of a proper showing of an unexpected and superior result over the disclosure of the prior art, no invention is involved in a result obtained by experimentation.”).

Thus, while patentability of an invention is not negated by the manner in which it was made, “the converse is equally true: patentability is not imparted where ‘the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success.’” Merck, 874 F.2d at 809 (quoting *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988)).

While we agree that the teaching of a prior art patent is not limited to its preferred embodiment, see Merck, 874 F.2d at 807 (“the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered”), the other amlodipine salts of which Apotex complains (i.e., amlodipine tosylate and amlodipine mesylate) were not expressly recited in the '909 patent or elsewhere in the prior art. Thus, the district court's obligation to consider the entire range of prior art compounds would have been satisfied here by its comparison of the closest prior art compound to amlodipine besylate. *Kao Corp. v. Unilever United States, Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (“[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.” (quoting *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)).

Another defect in the district court's reasoning is its failure to recognize that by definition, any superior property must be unexpected to be considered as evidence of non-obviousness. *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987). Thus, in order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected. Merck, 874 F.2d at 808. Here, Pfizer's evidence must fail because the record is devoid of any evidence of what the skilled

artisan would have expected. We will not simply presume that the skilled artisan would have expected that amlodipine besylate would have the same characteristics as amlodipine maleate, because as Pfizer asserts, its properties are not absolutely predictable. Further, Dr. Wells' testimony reflects the fact that he believed that amlodipine besylate would solve the problems of amlodipine maleate. Unrebutted testimony from Apotex's expert evidences that, given the range of 53 anions disclosed by Berge, one skilled in the art would expect those anions to provide salts having a range of properties, some of which would be superior, and some of which would be inferior, to amlodipine maleate. Pfizer has simply failed to prove that the results are unexpected. Boesch, 617 F.2d at 278.

The following legal principles with respect to obviousness can be derived from the above case law, which is a landmark judgment in recent times.

***Reasonable expectation of success and not a guarantee is needed***

In the present case, the patentee has a reasonable expectation of success in view of the valacyclovir literature available on the priority date of the impugned patent. Valacyclovir was found to be the most potent pro-drug of acyclovir which is also an antiviral drug. Thus, a skilled person having knowledge of the same did have a likelihood of success while trying monovaline esters of ganciclovir. As already mentioned hereinabove, it has been admitted by one of the Expert's that ester of acyclovir inspired them to test the esters of ganciclovir.

***Some degree of unpredictability in the art, does not make an invention non-obvious***  
***When a general approach seemed a promising field, and routine experimentation was required to be carried out in order to arrive at the subject matter, it does not render the subject matter nonobvious.***

The patentee has argued that other literatures taught away from mono-esters and the bioavailability associated with L-monovaline ester of ganciclovir was not at all expected. The opponent submitted that none of the literatures cited actually taught away from monoesters. The Martin et al publication annexed to the Mitscher affidavit, Stella affidavit and reply statement clearly go to show that in some scenarios bis-esters give better results while in others bis also gives worse results, and as bis-ester of ganciclovir was already tried, the Patentees tried with the second available option that is the monoesters and found the same to exhibit improved bioavailability. It is submitted that albeit there is an increase in the bioavailability of the monoester than that of ganciclovir per se or the bis-ester per se, trial and error

resulted in the same and such improvement was completely expected in light of the knowledge available to the Patentee at the priority date of the patent.

The most significant point in the present case is as under.

*“the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered”*

As the teaching of a prior art document is not limited to preferred embodiment, the Patentee's contention that bis-esters were more focused on in all the documents cited does not lessen their burden as to the show non-obviousness. The mono-esters were not taught away, i.e. none of the documents recited that using monoesters would be disadvantageous, even the teachings related to such less-preferred monoesters should be considered while determining nonobviousness.

The EPO Board of Appeals in case no. T 0051/97 - 3.3.1, held as under.

*Document (6) teaches to transform the  $\hat{\alpha}$ -modification of that particular azo dye into the  $\hat{\alpha}$ -modification thereof for improving its dispersion stability at high temperatures (page 2, lines 8 to 14; page 4, lines 19 to 24). The dispersion stable  $\hat{\alpha}$ -modification of that particular azo dye is prepared by heating the  $\hat{\alpha}$ -modification thereof dispersed in water (page 2, lines 16 to 24). Furthermore, the Respondent conceded that numerous azo dyes exist in different modifications and that therefore the teaching of document (6) is embedded and not unique in the field of azo dyes.*

*The Board concludes from the above that the state of the art, in particular document (6), gives the person skilled in the art a concrete hint as to how to solve the problem underlying the patent in suit as defined in point 2.3 above, namely by transforming the  $\hat{\alpha}$ -modification of the azo dye of formula (1) known from the closest prior art document (cf. point 2.2 above) into the  $\hat{\alpha}$ -modification thereof, thereby arriving at the solution proposed by the patent in suit. In the Board's judgement, it was obvious to try to follow the avenue indicated in the state of the art with a reasonable expectation of success without involving any inventive ingenuity.*

*The Respondent submitted that for the person skilled in the art the azo dye of document (6) was not structurally close enough to the azo dye of formula (1) known from the closest prior art to contemplate applying the teaching of that document to the latter azo dye. Moreover, in the light of the fact that numerous other azo dyes exist in different modifications, the character of that structural variation is considered by the Board to be insignificant with respect to variation of the*

morphology since the ethyl and the allyl group are both small aliphatic groups. For those reasons, the alleged lack of structural closeness of the azo dye of document (6) and that of formula (1), on which the Respondent's argument was based, is not supported by the facts.

Therefore, in the Board's judgement, the person skilled in the art is not diverted from translating but rather encouraged to translate the teaching of document (6) to the known  $\alpha$ -modification of the azo dye of formula (1), thus arriving at the  $\alpha$ -modification of that dye according to the claimed invention without involving any inventive activity.

#### **The EPO Board of Appeals in case no. T 0013/93 - 3.3.4, held as under.**

Document (1) relates inter alia to contacting plants, specifically sugar cane plants, with lactic acid and thereby achieving a growth different from that obtained for control sugar cane plants. It thus appears to the Board an appropriate starting point in the prior art for considering inventive step, and the Board considers no other document more relevant.

##### *Problem to be solved*

In relation to document (1), the problem that can be recognized is optimizing the composition of lactic acid when contacting sugar cane plants, such contacting being one of the possible applications covered by claim 1, with a growth or productivity stimulating amount of a plant growth composition of lactic acid.

##### *Inventive step*

The Board considers that the skilled person who has read document (1) with the information that the application of lactic acid will stimulate growth of sugar cane, and wishes to find out optimum conditions for this in practice, would, as a matter of routine, include testing the effect of both the racemate and the substantially pure L-(d)-isomer of Lactic acid, both of which were commercially available, on both roots and on the foliage of growing plants in order to collect information on precisely what compositions at what stages of growth produced optimum results. It appears to the Board that for sugar cane the skilled person would in an obvious manner starting from document (1) arrive at the conclusion that the area covered by Claim 1 produced optimum results.

The Board would emphasize that the correct approach to inventive step is not sure predictability of success drawn from given information in the prior art, but rather whether it would be obvious to try with a reasonable expectation of success. By way of balance, the Boards of Appeal have not required patentees to show with examples that there is certainty of success for everything claimed, but rather the Boards are prepared to make assumptions that this is so on the basis of evidence showing that success is plausible.

#### **The EPO Board of Appeals in case no. T 1344/05 - 3.3.02, held as under.**

*Thus, the question to be answered is whether the proposed solution, i.e. the replacement of the solvent ethanol by benzyl alcohol, was obvious to the skilled person in the light of the prior art.*

*In that respect, the Board observes that document (3) discloses formulations containing benzyl alcohol, glycerol formal and the drug abamectin (examples 3 to 7).*

*Moreover, the patent in suit itself indicates that "among the tested solvents proved suitable Ethanol, Benzyl Alcohol and GLYCEROL FORMAL Ethanol and Benzylic Alcohol are already used as solvents for parenteral administration of drugs..." (page 3, lines 7 and 8).*

*Accordingly, as the skilled person is free, for the purpose of preparing of a further formulation, to choose any solvent which is prima facie suitable for the intended use, the Board is satisfied that the skilled person would replace the solvent ethanol disclosed in document (1) by another alcohol, namely benzyl alcohol, without an inventive step being involved, since both document (1) and the patent itself make it clear that benzyl alcohol is a solvent suitable for use in the parenteral administration of drugs.*

The above cases corroborate the obvious to try principle.

In the present case, the patentee has a reasonable expectation of success in view of the valacyclovir literature available on the priority date of the impugned patent. Valacyclovir was found to be the most potent pro-drug of acyclovir which is also an antiviral drug. Thus, a skilled person having knowledge of the same did have a likelihood of success while trying monovaline esters of ganciclovir. As already mentioned hereinabove, it has been admitted by one of the Experts that valacyclovir inspired them to test the esters of ganciclovir.

The opponent also states that Exhibit 8/Exhibit K annexed to Mitscher Affidavit and Stella Affidavit taught that both bisesters and monoesters showed poor bioavailability thereby asserting the fact that bisesters are not always better than the monoesters and it is a matter of routine optimization to find out which of the esters have superior activity, as the bis-valine ester of ganciclovir is already tried and tested, the obvious alternative for the patentee was to try the mono ester which expectedly showed improved bioavailability.

**The EPO Board of Appeals in case no. T 0393/01 - 3.3.2, held as under.**

Optimization

*As regards the first aspect, document (9), shows precisely that IPC is a more effective biocide than IPBC (see comparative example in example 2, table II).*

The opponent also states that Exhibit 8/Exhibit K annexed to Mitscher Affidavit and Stella Affidavit taught that both bisesters and monoesters showed poor bioavailability thereby asserting the fact that bisesters are not always better than the monoesters and it is a matter of routine optimization to find out which of the esters have superior activity, as the bis-valine ester of ganciclovir is already tried and tested, the obvious alternative for the patentee was to try the mono ester which expectedly showed improved bioavailability.

**The EPO Board of Appeals in case no. T 1101/98 - 3.3.4, held as under.**

*The difference between the derivatives described in document (1) and the claimed compounds resides in the nature of the substitution on the nitrogen of the fructopyranose sulfamate, as the earlier derivatives are methyl or phenyl derivatives (see point 1, above) whereas the latter carry an imidate group.*

*Document (2) describes the advantages associated with chemically transforming drug substances into per se inactive derivatives (prodrugs), in particular, that the prodrug reconverts to the drug in vivo, so that the prodrug possesses, albeit indirectly, the same pharmaceutical properties as the drug, and, also, that the prodrug may be the solution to delivery problems due to e.g. unfavourable solubility and lipophilicity.*

*the light of document (2), would turn to isolating prodrugs as these would be expected to convert to the active parent drug in the body system. The Board accepts that it could not be predicted with certainty whether, in vivo, imidate derivatives of fructopyranose sulfamate would be toxic or not, nor whether they would undergo satisfactory hydrolysis. Yet, the combined teachings of documents (1) and (2) would lead the skilled person in an obvious manner to make imidate derivatives and testing them would be a matter of routine as shown in document (1) which discloses that the anticonvulsant activity test is a standard test dating from 1952 (page 881, right hand column, "Anticonvulsant testing").*

*There is, thus, no inventive activity linked to preparing or testing these compounds.*

The above case also deals with prodrugs and was found to be obvious in light of the knowledge available to a skilled person by way of Documents D5. In the present case to,

there were umpteenth documents available on prodrugs Notari et al, also the documents on Valacyclovir which is a monovaline ester(prodrug) of acyclovir which provided enough impetus and motivation to a skilled person to try monovaline esters of ganciclovir.

7.17 Thus, in view of the above submissions and the case laws relied upon by the opponent the impugned patent ought to be revoked under Section 25(2)(e).

#### **8. Section 25(2)(f): NOT AN INVENTION/NOT PATENTABLE**

Under Section 3(d)

8.1 L-valine monoester of ganciclovir is a prodrug of ganciclovir as admitted by the patentee itself in the specification and as evident from the Label Information of Valcyte. Prodrugs as defined hereinabove as inactive substances (for present case no antiviral activity) which act as vehicle to carry the drug to the site of action. Due to this mechanism of action, the active metabolite is more bioavailable at the site of action than when the drug itself is delivered orally and is thus similar to the intravenous delivery of the drug the antiviral activity of the drug remaining the same. It is apparent from the label information as well as the Ljungman Affidavit that the pharmacokinetic property of the prodrug is similar to that of the intravenous ganciclovir. **The impugned invention claims a prodrug which is a monoester and from Section 3(d) refers esters as same as the substance per se unless they differ significantly in terms of efficacy, which has been defined by the Hon'ble Madras High Court as therapeutic efficacy. In the present case the monoester differs from the substance ganciclovir by bioavailability and such property cannot render efficacy to the said ester to qualify as a different compound.**

8.2 It has also been mentioned by the opponent that the compound in claim 4 claims a crystalline form which is barred from patentability under Section 3(d) of the Act unless it exhibits enhanced efficacy. It is submitted that if we take into consideration the submissions made at the USPTO during the prosecution of the corresponding US application, it is quite apparent that the patentee admits that the monovaline esters are disclosed in Beauchamp (D6) but not the crystalline form. **Thus, for a proper efficacy**

determination under Section 3(d), the patentee ought to have compared the crystalline form over the monoester form disclosed in Beauchamp.

**The Ld. Controller in the matter of 1440/MAS/1998, held as under.**

*The explanation under Section 3(d) reads as;*

*"For the purpose of this clause, 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".*

*Therefore it was prayed not to equate the crystalline forms with the amorphous form as crystalline forms are the pure form of a known substance which is proven to be more efficacious and hence the present invention do not attract the provisions of Section 3(d) of the Patents Act hence the grant of patent right is requested.*

*Though the arguments are impressive from the applicant and opponent the alleged invention should be judged according to the provisions laid under the Patents Law. Section 3(d) emphasizes that a new form of a known substance is patentable unless the new form shows enhancement in the **KNOWN EFFICACY** of the known substance. The next question is what is known efficacy? Efficacy of a pharmaceutical, in pharmacology, as defined in Dorland's Illustrated Medical Dictionary is the ability of a drug to produce the desired therapeutic effect and it is independent of potency, which expresses the amount of the drug necessary to achieve the desired effect.*

*In the entire description of the invention the therapeutic effect of the crystalline forms is not disclosed. Hence it is concluded that the crystalline forms exhibit the same efficacy as the amorphous form.*

*I do not agree with the applicant's view that only any crystalline form is the purest form of an amorphous form of a pharmaceutical. Even if it is considered that crystalline forms as pure form, still the application is silent in showing or proving the enhancement in known efficacy.*

*Therefore the applicant has failed in proving that the alleged invention does not attract the provisions under Section 3(d) of the Patents Act.*

In the present case too, the therapeutic effect of the crystalline L-monovaline ester of ganciclovir is not found to assert the fact that crystalline form has enhanced efficacy. Following the reasoning of the above decision, the present claims ought to be rejected under Section 3(d).

**The Ld. Controller in the matter of 2485/DEL/1998, held as under.**

*The position therefore is, if the discovery of a new form of a known substance must be treated as an invention, then the patent applicant should show that the substance so discovered has a better therapeutic effect. Dorland's Medical Dictionary defines the expression 'efficacy' in the field of pharmacology as 'the ability of a drug to produce the desired therapeutic effect and 'efficacy' is independent of potency of the drug Dictionary*

meaning of disease/having a good effect on the body Novartis Annexure 1 of para 13. Improved particle size stability, at most, means that someone who chooses to manufacture nevirapine in an aqueous solution would benefit from being able to store the medicine for longer periods of time. However, the therapeutic effect of nevirapine whether in hemihydrates form or anhydrous form or whether administered in aqueous tablet parental or any other dosage form would remain unchanged. The applicant has failed to place on record any evidence to show that the therapeutic effect of nevirapine hemihydrates in aqueous solution is significantly enhanced over other known forms of nevirapine. As such, Claims 1, 2 and 5 are invalid and fall under Section 3(d).

I have analyzed the above arguments and have come to the conclusion that the product (composition) claims fall under section 3(d) of the Patents Act in the absence of any data for the composition to show enhanced efficacy.

Therefore, I conclude that the product claims fall under section 3(d) as they are all a combination of known substances and this section clearly mentions that only if enhanced efficacy can be established such compositions would be allowed to be claimed.

8.3 However, in the instant case the only improved property shown by the prodrug is that of bioavailability and the opponent submitted that bioavailability of a drug is not directly related to the therapeutic efficacy of the drug and the same has been held in the below decisions of the Indian Patent Office.

8.4 The opponent cited paragraph 13 of the judgment of the **Hon'ble High Court of Madras in the case of Novatis Ag Vs. Union Of India (UOI) & Ors("Novartis case" in short)**; wherein efficacy and therapeutic effect has been described and defined.

*"As we understand the amended section, it only declares that the very discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance, will not be treated as an invention.*

*The position therefore is, if the discovery of a new form of a known substance must be treated as an invention, then the Patent applicant should show that the substance so discovered has a better therapeutic effect. Darland's Medical Dictionary defines the expression "efficacy" in the field of Pharmacology as "the ability of a drug to produce the desired therapeutic effect" and "efficacy" is independent of potency of the drug. Dictionary meaning of "Therapeutic", is healing of disease - having a good effect on the body." Going by the meaning for the word "efficacy" and "therapeutic" extracted above, what the patent applicant is expected to show is, how effective the new discovery made would be in healing a disease / having a good effect on the body? In other words, the patent applicant is definitely aware as to what is the "therapeutic effect" of the drug for which he had already got a patent and what is the difference between the therapeutic effect of the patented drug and the drug in respect of which patent is asked for. Therefore it is a simple exercise of, though preceded by research, - we state - for any Patent*

*applicant to place on record what is the therapeutic effect / efficacy of a known substance and what is the enhancement in that known efficacy. The amended section not only covers the field of pharmacology but also the other fields”.*

In the present matter, no data is available in the specification which shows that the allegedly claimed compound can mitigate the disease in a better way than the parent drug. The opponent submits that the Patentee's expert, Dr. Ljungman has made an observation that the pharmacokinetic properties of valganciclovir is similar to intravenous ganciclovir than oral ganciclovir”. Thus the allegedly claimed compounds do not have any enhanced efficacy over intravenous ganciclovir and ought to be rejected under Section 3(d) of the Act.

**The Ld. Controller in the matter of 729/DEL/1998, held as under.**

*The methanesulfonate hydrate must differ significantly in properties with regard to therapeutic efficacy from which the derivative is made. The description of the claimed invention in complete specification in the light of arguments and Exhibits submitted by the opponents as discussed in para 6.6 does not describe anything relevant that can show "new derivative (hydrates) differ significantly in properties with the known generic compounds". The data provided by the applicant for the gemifloxacin Mesylate hydrate does not show any enhanced therapeutic efficacy over the parental compound known in the art. Comparative tests relating to therapeutic efficacy for the hydrate form where  $n = 1.5$  and  $n = 3$  vis-i-vis the closest prior art has not been provided. Further on page 8 of the instant specification it is admitted that the methanesulfonate and its hydrate exhibit the same potent antibacterial activity as the corresponding free base disclosed in 8P688772.*

In the present case too, no data has been adduced by the patentee to show that superior bioavailability is related to therapeutic efficacy. Ganciclovir and valganciclovir as claimed in the present invention has the same antiviral activity, the only difference is that the prodrug facilitates the transport of the compound to the site of action. It has been admitted by the Patentee's expert Dr. Ljungman says (page-14, point 48) “pharmacokinetic properties of valganciclovir is similar to intravenous ganciclovir than oral ganciclovir”.

Thus the present claims ought to be rejected under Section 3(d) of the Act.

**The Ld. Controller in the matter of 3598/DELNP/2004, held as under.**

Therefore if the improvement brought about in the new form of the basic substance is substantially more in therapeutic value, only then such form i.e. pseudo polymorphs in the present case would be allowed u/s 3(d) of the Patent Act 1970. The applicant has completely failed to show any significant therapeutic efficacy in their polymorphs (ethanolate & hydrate) in the body of specification or subsequently in the expert's affidavit. The applicant has rather shown the enhancement of bioavailability in the Han's affidavit by way of blood

I am not very much convinced with the logic of Joel's statement that "... healing effect is enhanced over generic potential of the molecular entity by providing a crystal form of formulation, storage and ultimate administration, which in the eye of the inventor, after the expense of considerable effort, has the best combination of stability, solubility and bio availability of crystal form" because the requirement u/s 3(d) of the Patent Act 1970 is only significant enhancement of therapeutic efficacy compared to the generic molecule and not the enhancement in the physico chemical properties in the form of stability and bio availability.

Pseudo polymorphs, namely the ethanolate and the hydrate are merely different physical form which may be stable and due to higher bio availability may readily available at the site of action i.e. in blood plasma, but do not increase or improve the action of the drug in terms of mitigating the disease in general or improving protease inhibitory activity in particular. In other words, such

improvement in stability and bio availability do not, contribute to the therapeutic nature of the drug or alter therapeutic profile of the drug compound as compared to the generic compound.

Therefore on the basis of above analysis made by me in the preceding Para, I am of the considered view that the applicant has completely failed to fulfill the requirement of section 3(d) of the Patent Act 1970.

**The last three paragraphs reproduced above is of utmost importance in the present case, it is submitted that the prodrugs/L-monovaline esters of ganciclovir make the**

parent drug i.e. ganciclovir more bioavailable. As to the improvement in bioavailability, the same makes the drug readily available at the site of action but do not contribute to the therapeutic nature or the therapeutic profile of the drug. the therapeutic activity of the drug remains the same as intravenous ganciclovir.

Thus the present claims ought to be rejected under Section 3(d) of the Act.

**The Ld. Controller in the matter of 1122/DEL/1995, held as under.**

*(HF) Issue of sec 3 (d); The opponent in the representation parag.3 has raised the issue of disallowance of the claims u/s 3(d) of the patents act. The opponent argued during hearing that the applicant has not provided any data in the specification to justify, the efficacy of the mildly modified combination of the substances to make the multiple unit tableted dosage form over the already known art i'e' as disclosed in Exhibit land discussed above. The applicant rebutted the argument with the statement that the applicant has given the efficacy data in enhancement of the properties as enhanced acid resistance in tablet on page 37 of Specification'. In this regard I observed that the applicant has failed to provide any data regarding therapeutic efficacy of the dosage form as claimed in claims 1 to 10 and 13,14. I rely on the judgment dated 6th Aug 2007 of the Hon,ble High court of Madras in Novartis Vs UOI case where the efficacy as indicated in sec 3 (d) has been defined as the therapeutic efficacy. The therapeutic efficacy can be substantiated by providing data regarding the clinical trials of the medicinal combination Dosage form. In view of this fact I conclude that the Claims are not Patentable U/s3(d) of the Patents Act.*

*(HG)In the light of the aforesaid discussion I refuse to grant the patent on the application no. 1122/Del/1995 due to theinvention as claimed in revised claims from 1 to 17 is not having any inventive step and not Patentable U/s 3 (d)'*

In the present case too, the patentee has failed to show the prodrug, which has superior bioavailability helps mitigate the disease. In absence of such data, the patent ought to be rejected under Section 3(d).

**The Ld. Controller in the matter of 2076/DEL/1997, held as under.**

*( G) -Not an invention: I t is clear from previous discussions that invention is not patentable' under section 2(1) ( j ) anso t involving n y invent ivest ep.*

*( C-1) SECTION 3(d) it t may be seen from the description in complete specification of impugned application that the basic aim of the application is to improve the nucleotide eM PA in such away that it may be chemically able to ensure an adequate shelf life ,proper biodistribution and bioavailability upon oral administration so that the*

therapeutic effect so f PMPA(nucleotide analog) may be delivered more effectively to the subject. The subject as per the description appears to be beagle dog. In the trials relating to estimation of bioavailability, the activity and potency selectivity in mice have been carried out on dogs. There is no data available for estimating the therapeutic efficacy. The enhanced therapeutic effect so, in beagle dog venA. In data provided relates to the enhanced properties of the prodrug "carbonate carbamate PMPA". The complete specification of impugned specification is and is closing the dosage to the human on page 35 line 10-15 but not initial to check the improvement of the Drug which is treating the human being and enhancement in therapeutic effect have been provided by the applicant.

There is no comparison available in the complete specification and no such document was as provided during hearing which gives an idea about the enhanced therapeutic effect so f carbonate/carbamate prodrug of PMPA and PMPA as claimed on dogs and/or on human.

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The intention of the legislation encompassed in section 3(d) of the Patent Act is usually, in the product patent particularly the pharmaceuticals product in India should be granted with utmost care and should be granted only to very genuine cases. Therefore, a clear bar of showing efficacy has been imposed to Patent the products particularly the Pharma products. The Hon'ble High Court of Madras in the decision of Novartis vs. UOI, dated 06/08/2007 has defined the therapeutic efficacy as efficacy for pharmaceutical products. The Hon'ble High Court of Madras held that:-

'As we understand the amended section it only declares that the very discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance will not be treated as an invention. The position therefore is, if the discovery of a new form of a known substance must be treated as an invention then the patent application should show that the substance so discovered has a better therapeutic effect . . . . . in other words, the patent applicant is definitely aware as to what is the 'therapeutic effect of the drug for which he had already got a patent and what is the difference between the therapeutic effect of the patented drug and the drug in respect of which patent is asked for . . . . . The explanation creates a deeming fiction that all derivatives of a known substance would be deemed to be the same substance unless it differ significantly in properties with regard to efficacy. . . . '.

( G 2 ) Process claims and Section 3(d) : The process claims 19 to 22 and 24 relate to the compound falling under definition of "known substance" as defined in section 3(d) therefore the compound prepared by the process as claimed in the claims mentioned above is not patentable. The ingredients used by the process are well known according to the prior art documents D1 - D3, D6 for masking the phosphonate group of PMPA as discussed above therefore the process is also not patentable under section 3(d).

**The Ld. Controller in the matter of 2076/DEL/1997, held as under.**

( G 3 ) DECISION ON PATENTABILITY/US 3(d) : The claims 1 to 24 relating to the compound falling under definition of "known substances" as defined in 20

section 3(d) therefore the compound itself and the process for preparation as claimed in the claims is not patentable under section 3(d). Therefore I conclude that the derivatives as claimed in the impugned application and process for preparation thereof is mere discovery of a new form of a known substance PMPA and mere use of the known process which does not result in enhancement of the known efficacy of that substance and hence are not patentable under section 3(d) of the Patents Act, 1970.

**NON PATENTABILITY:** It the opponents and arguments is observed from the aforesaid of both the parties that the claimed invention is an ester derivative of the primary compound pMpA as well as it is a prodrug of PMPA. Such compounds in order to be patentable tils 3 (d) need to show the improved efficacy. The Hon'ble High Court of Madras has defined the term efficacy in cases of pharmaceutical compounds as the therapeutic efficacy which can be established by the clinical trial results of the new form of Drug. The Data provided by the applicants is related to the improved properties of the compound of the present invention. There is no evidence and data in specification to prove the improved clinical efficacy of the claimed pharmaceutical substance as compared to its own base drug moiety PMPA. Moreover whatever is the improvement is in the properties of the impugned product which is expected only as is evidenced by the results of the conversion of the compounds of same group as mentioned in the discussion and arguments given above.

The complete specification of impugned specification is disclosing the dosage to the human on page 35 line 10-15 but no clinical trial to check the improvement of the Drug while treating the human being and enhancement in therapeutic effects have been provided by the applicant.

There is no comparison available in the complete specification and no such documents as provided in the hearing which gives an idea about the enhanced therapeutic effects of carbonate/carbamate prodrug of pMpA and pMpA as claimed on dogs and/or on human. The intention of the legislation encompassed in section 3(d) of the patent Act is very clear the product patent particularly the pharmaceutical product in India should be granted with utmost care and should be granted only to very genuine cases. Therefore a clear bar of showing efficacy has been imposed to patent the products particularly the Pharma products. The hon'ble High Court of Madras in the decision of Novartis vs. Union, dated 06/08/2007 has defined the therapeutic efficacy as efficacy for pharma products. The Hon'ble High Court of Madras held that :—

'As we understand the amended section it only declares that the very discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance will not be treated as an invention. The position therefore is, if the discovery of a new form of a known substance must be ) ) treated as an invention then the patent application should show that the substance so discovered has a better

therapeutic effect . . . . . in other words, the patent applicant is definitely aware as to what is the therapeutic effect of the drug for which the had already got a patent and what is the difference between the therapeutic effect of the patented drug and the drug in respect of which patent is asked for . . . . . The explanation create as deeming fiction that all derivatives of a known substance would be deemed to be the same substance unless it differ significantly in properties with regard to efficacy....., Process claims and Section 3(d): The process claims 19 to 22 and 24 relate to the compound falling under definition of "known substance" as defined in section 3(d) therefore the compound prepared by the process as claimed in the claims mentioned above is not patentable. The ingredient used by the process are well known to a person skilled in the art for preparing such esters of the pharma compound N' o'specifsicte p have been characterized by the applicant so as to establish that the process is patentable U/s 3(d) of the patents Act. In view of the aforesaid discussion the claims 1 - to 24 relating to the compound falling under definition of "known substances as defined in section 3(d), the compound it self and the process for preparation as claimed in the claims is not patentable under section 3(d). The derivatives as claimed in the impugned application and process for preparation thereof is mere discovery of a new form of a known substance PM PA and the process is mere use of the known process to produce a known product which does not result in significant enhancement of the known efficacy compared to the base molecule of that substance and hence are not patentable under section 3(d) of the patents Act, 1970

In both the above cited decisions, the application relate to carbamate and carbonate forms of PMPA, which are nothing but prodrugs. The applicant submitted data on bioavailability but there was no data to estimate the therapeutic efficacy, all data provided relates to enhanced efficacy. Thus, bioavailability was considered to be a property which cannot be related to enhanced efficacy. Applying the facts of the above cases to the present case would render the L-monovlaine ester of ganciclovir non-patentable under 3(d) in a similar manner.

**The Ld. Controller in the matter of 896/DEL/2002, held as under.**

(F.3) not patentable U/s 3(d) : It has been observed that the opponent alleges impugned invention falls U/S 3(d) as the basic compound BIS( POCP)MPA is already known before the priority date of the impugned application. The impugned application has provided the Fumarate salts of the Bis(poc)pMpA which is a salt of known substance under the definition of sec3 (d) .The applicant had the duty to prove that the Fumarate salt showed significant improvement is properties with regard to efficacy. I rely on the judgment dated 06-08-2007 of the Hon'ble High Court of Madras in Novartis v UOI case where the efficacy in r/o the pharmaceutical substance have been defined as therapeutic efficacy which may be proved by providing clinical trails of the newly developed substan ce.

*It has been observed that the impugned application does not depict any clinical trial results to prove that the newly formed fumarate salt is more efficacious than Bis(Poc)P MPA in terms of therapeutic effects. Whatever is shown in details as the so-called improvements in the properties, do not amount to an enhancement of therapeutic effect. In the light of all the above discussed I hold that the invention as claimed in the impugned application falls under Section 3(d) and hence not patentable.*

The above decision is on an application related to pro-drugs. The improvements shown by the applicant were not found to be enough in view of the available knowledge and the expected improvement. In the present case too valganciclovir, which is a prodrug of ganciclovir improves the bioavailability of ganciclovir which is wholly expected in view of the various prior art documents cited thus the present patentee does not show any significant increase so as to be rendered patentable under Section 3(d).

8.5 Regarding reduction of toxicity, it is submitted that there is no data in the specification of the impugned patent to establish low toxicity. On the contrary, on going through the label of Valcyte, particularly the pages specified under the ground of obviousness, it would be clear that the toxicity profile of L-monovaline ester of ganciclovir is same as ganciclovir itself.

#### **Process claims**

8.6 The opponent submitted that the process claims of the instant patent are not patentable under Section 3(d) as the reactants used, the process of preparation and the end product obtained are not new and ought to be rejected. The protection and the deprotection are taught in prior art as mentioned above, and so is the bis valine ester. The isolation steps are also conventional as admitted by the patentee in the specification. The opponent submitted that claim 10 is the principal process claim and claim 11 specifies the conditions for carrying out the removal of the amino acid hydroxy-protecting groups.

8.7 The opponent submitted that Harnden et al teaches a scheme at page 1749 which goes to show that the process of esterification of free base as well as the formation from the bis ester.

The specification at page 35 also discloses that isolation of the monoester by conventional methods and separation of the unreacted amino acid so that bis is not formed

The specification at page 38 also discloses that the compound can be prepared from the bis-valinate of ganciclovir as exemplified in eg. 5 of D5 by partial hydrolysis which again is a known process.

8.8 The patentee has also failed to provide any efficacy data with regard to the process in the specification. Therefore the present claims fall under Section 3(d) of the Patent Act and ought to be revoked. The opponent cited the following cases to support its contention on the ground that the inventions are not patentable under Section 3(d) of the Act.

**The Ld. Controller in the matter of 2076/DEL/1997, held as under.**

*Process claims and Section 3(d): The process claims 19 to 22 and 24 relate to the compound falling under definition of "known substances" as defined in section 3(d) therefore the compound prepared by the process as claimed in the claims mentioned above is not patentable. The ingredients used by the process are well known to a person skilled in the art for preparing such esters of the pharma compound. No specific step has been characterized by the applicant so as to establish the process is patentable U/s 3(d) of the patent Act.*

*In view of the aforesaid discussion the claims 1 to 24 relating to the compound falling under definition of "known substance" as defined in section 3(d), the compound itself and the process for preparation as claimed in the claims is not patentable under section 3(d). The derivative as claimed in the impugned application and process for preparation thereof is mere discovery of a new form of a known substance PMPA and the process is mere use of the known process to produce a known product which does not result in significant enhancement of the known efficacy compared to the base molecule of that substance and hence are not patentable under section 3(d) of the patents Act, 1970.*

**The Ld. Controller in the matter of 2076/DEL/1997, held as under.**

*(G 2) Process claims and Section 3(d): The process claims 19 to 22 and 24 relate to the compound falling under definition of "known substance" as defined in section 3(d) therefore the compound prepared by the process as claimed in the claims mentioned above is not patentable. The ingredients used by the process are well known according to the prior art documents D1 - , D3, D6 for masking the phosphonate group of PMPA as discussed above therefore the process is also not patentable under section 3(d).*

Thus the impugned patent ought to be revoked under Section 25(2)(f) as the subject matter is not an invention and hence non-patentable under Section 3(d).

## 9. PATENTEE'S CASE ON ANTICIPATION

### *1. Anticipation*

The patentee rebutted by submitting that the formula of the compounds as claimed in D5 is found at line 39 at column 1 of the patent document. Column 2, lines 13 to 36 deal with the various preferred salts, esters of the compounds as claimed in D5.

The patentee then handed out a EPO document on the two list principle. The patentee submitted that in the present case the disclosure has several lists, 8 in particular which in turn has various alternatives from which the patentee had to select the compound as claimed in the impugned patent.

The 8-lists is as under.

1. Cytosine or Guanine
2. 20 Naturally occurring aminoacids/ other non-naturally occurring amino acids
3. neutral amino acids which are 12 in number
4. Preferred aliphatic amino acids
5. aliphatic amino acids having upto 6 carbon atoms
6. 4 examples of amino acid given, they are just examples and not preferences
7. Mono & diesters
8. pharmaceutically acceptable salts (as found in line 32 at column 2)

According to the patentee that a combination of the various species in the 8 lists would give millions of compounds, 1000s and 492 at the least and handed out sheets showing the various alternatives that have to be selected for each group from the formula of D5 to arrive at the impugned patent.

Thus, in light of the two-list principle, the D5 discloses 8 lists and hence there is no disclosure of L-monovaline ester of ganciclovir.

The patentee submitted that the enabling disclosure as determined by the opponent is completely based on assumptions and a skilled person would not make such assumptions. The patentee submitted that the opponent mainly argued on the basis of inherent

anticipation, which was not found in its written pleadings. The patentee submitted that there was no inherent anticipation as D5 does not teach the process of preparing monovalyl ester of ganciclovir.

The patentee also cited two patent applications made by Cipla Ltd and Ranbaxy Ltd., wherein the following was mentioned.

Cipla patent application:

The patentee referred to the following portion

“Though the Bis-L- valyl ester prodrug of ganciclovir with a better bioavailability profile is mentioned in European Patent Application 0375329, it does not disclose any details of utility or preparation for mono L- valyl ester of ganciclovir”.

Ranbaxy application

The patentee referred to the following portion

“European Patent No 375329 discloses diester prodrugs of ganciclovir and physiologically acceptable salts thereof having improved bioavailability when administered through oral route”

According to the Patentee, these patent applications reassert the fact that mono esters were not taught in D5.

The patentee also cited Winkler et al , Dr. Mitscher’s affidavit which discusses D6/D5 to show that the common general knowledge available to a skilled person at the priority date of the invention would not permit a skilled person to carry out the present invention.

**The Patentee presented a few case laws on the ground of anticipation.**

## **10. OPPONENT’S REBUTTAL ON ANTICIPATION**

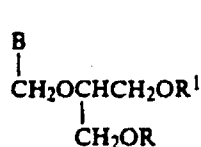
**10.1 The patentee 8-list principle is completely baseless as to the facts of the present case. It was submitted that the two or more list principle is applied under the EP law specifically to selection inventions. Selection inventions deal with the selection of individual elements, sub-sets, or sub-ranges, which have not been explicitly mentioned, within a larger known set or range, but the selected group has some unexpected property which renders it nonobvious and renders it eligible for a patent.**

Thus, the patentee's argument based on the list principle is completely wrongly founded. The patentee did not have a case of selection invention made in its written pleadings. Moreover, it is submitted that the patentee's reliance on such 8-list principle is in fact an implicit admission that the monoesters were implicitly disclosed in D5, if not explicitly. **Moreover if selection patent is argued by the patentee there has to be admission of lack of novelty, since selection occurs from known area.**

10.2 The opponent would also like to point out one more flaw in the patentee's submissions. The patentee listed the amino acids, aliphatic amino acids, neutral amino acids and four specific amino acids under separate lists, it is submitted that these are not different lists, i.e., they do not refer to alternate species but are sub-species belonging to the same group. The patentee has erroneously listed the preferred groups as different groups and increased the so called list to fit their purpose.

10.3 The opponent maintains its submission on the ground of anticipation vis-à-vis enabling disclosure and states that the patent under opposition lacks novelty.

10.4 The opponent referred to the structure of the compound as disclosed in line 39 at column 1 of D5 was drawn and the substituents were mentioned.



The opponent submitted that in total there are 3 substituents in the structure as disclosed in line 39 of column 1 of D5. The patentee's first list was that of the choice of B from one of the two substituents. It is submitted that the patentee did not have to choose between cytosine and guanine as they worked on improving bioavailability of ganciclovir as admitted in the impugned specification. Thus, B always have to be guanine.

With respect to the other substituents, i.e., R and R<sup>1</sup>, it was submitted substituting any one of R or R<sup>1</sup> by a amino acid ester would yield mono amino acid esters of ganciclovir. Moreover it is clearly mentioned that "at least one of R and R<sup>1</sup> represents an amino acid acyl residue". This clearly points out to the mono ester

being disclosed in /D5. The preferred amino acids were also mentioned in line 23 at column 2 which includes valine out of the four examples. The amino may be in L and D form, the most preferred being L-amino acids. The preferred salts in hydrochloride salts. Thus, the entire product claim of the impugned patent is disclosed in /D5, and it only remains and its only remains to be decided whether such disclosure is enabling or not. The opponent has herein above shown that there is enabling disclosure herein before and hence the compound of claim 1 is anticipated by /D5.

10.5 It was also pointed out that the diastereomers as claimed in claim 1 was not argued by the patentee.

10.6 The opponent pointed out that Dr. Mitscher in its expert affidavit, paragraph 56 clearly mentioned that the /D5 did not teach the isolation of the monoesters. It is quite evident from his statement that /D5 therefore does not disclose the isolation process, which otherwise can be done by a reasonably skilled person without undue experimentation, therefore the disclosure in /D5 amounts to enabling disclosure which anticipates the L-monovaline ester of ganciclovir. Moreso since the patentee has admitted in the specification that the isolation is by conventional methods and the patentee at the hearing did not rebut or argue against the same.

10.7 The opponent also submitted that the **impugned specification also teaches that example 6(b) of /D5 teaches a mixture of 90% bis esters and 10% monoester of ganciclovir.** Thus, the arguments made at the hearing vis-à-vis disclosure is in complete departure to its reply statement as well as the specification.

10.8 The opponent pointed out that none of the cases cited by it on the ground of anticipation was dealt by the patentee and the only contention was that there is no disclosure in /D5. Thus, the main thrust of its argument was on the ground that D6/D5 had no disclosure of L-monovaline ester of ganciclovir. Thus, if it can be shown that said

compound is disclosed by way of enabling disclosed the product claims of the impugned patent are anticipated.

**10.9 The opponent also submitted that mosaicing was certainly not applicable in the present case since the opponent relied upon only D5 to establish lack of novelty.**

The case laws submitted by the patentee are not at all applicable to the facts and circumstances of the present matter for reasons stated hereinbelow.

In the case of **Apotex v. Sanofi, the Canadian Court** found that the prior art patent could encompass around 250,000 compounds (pg. 5 of judgment) and finding the appropriate compound from a group of 250,000 was found to require undue experimentation which fell outside the scope of common general knowledge. As submitted by the Patentees themselves around 1000 compounds are encompassed in the disclosure of D5 and a least of 492 compounds.

However as submitted in detail by the opponent under the ground of Section 25(2)(b), the monoester, in the present case, can easily be derived from the example 5 of the bis-valinate ester read with the disclosure that both mono and bis esters have improved bioavailability as mentioned in D5 which requires no undue experimentation. Thus, the facts of both the cases are completely different and hence not applicable in the present case.

#### **Pfizer Canada v. Canada**

The opponent submitted that the D5 does not teach a broad class of genus of compounds, it teaches the bis-esters and also monoesters which has also been admitted by the patentees. It covers both mono and bis esters and particularly exemplifies the bis-valinate ester of ganciclovir from which mono ester can be easily prepared without the exercise of inventive skill. D5 contains clear directions as to how the monoesters can be obtained. The opponent thus submit that this case is in fact supporting the submissions of the opponents.

**Lallubhai chakubhai Jariwala v. Chinmanlal Chunilal and Co.**, paragraph 10 of this judgment was placed which requires that for sufficiency of a prior publication for constituting prior knowledge, the sufficiency has to be determined on the basis of the entire document. The opponent submits that D5 taken as a whole alongwith common general knowledge would enable a person to carry out the present invention.

The **Supreme Court judgments** placed for supporting the proposition that the cardinal principal of interpretation of Statute when no specific meaning is mentioned in the statute is to take the natural meaning.

The opponent submitted that these cases do not hold in the present case as the term efficacy has been already interpreted by the Madras High Court in the Novartis case which still stands as good law.

Thus, the interpretation of the term efficacy remains the same as interpreted by the Madras High Court as mentioned hereinabove under the ground of 3(d)

#### **11. PATENTEE'S CASE ON OBVIOUSNESS**

Regarding obviousness, the patentee has made the following submissions:

Annexure 1: Notari et al

- This paper generally talks about prodrug esters.
- does not talk about ganciclovir.
- Does not teach amino acid esters of ganciclovir
- Does not teach monovaline esters of ganciclovir

The patentee submitted that the Annexure 1 was published in 1981 and Beauchamp et al and Martin et al, which were published in between the 1981 and the priority date of the invention all had knowledge of the Notari document (annexure 1) but still taught away from the same.

Annexure 2:

Teaches famciclovir and Penciclovir

Valyl mono ester of ganciclovir not taught.

Compound No. 15 – Monoester

17 – Monoester

Rest of the compounds are bisesters: compound no.14 & 16)

The document teaches that 14 and 16, the bisesters were selected for further studies. Thus document teaches away from monoesters.

Annexure 3:

Does not refer to ganciclovir or monoester or amino acid monoesters or to L-Valine monoesters.

Article does not consider toxicity issues.

It is quite apparent from the title of the paper that the document deals with tris and bis esters which in no way motivate the present invention.

Annexure 4:

Relates to Famciclovir and not to ganciclovir.

Annexure 5:

Pertains to penciclovir and does not teach amino acid monoesters.

There is no oxy- group in the purine group or the aliphatic chain unlike the present invention.

Jenson et al: the patentee submitted that it is an admitted prior art pertaining to ocular or parenteral administration

Colla et al relates to acyclovir and not ganciclovir. Acyclovir can form only monoesters as its structure permits the formation of only one ester. Therefore, such document cannot motivate the present inventors.

Beauchamp – 1992- mentions that ganciclovir has drawbacks related to the low bioavailability and high toxicity

Exhibit 7:

Does not teach about amino acid mono esters

According to column 1 at pg 819, the drug is administered intravenously whereas the present formulation is an oral one and hence it does not lead or motivate a skilled person to try amino acid monoesters of ganciclovir.

## **12. OPPONENT'S REBUTTAL ON OBVIOUSNESS**

**12.1 The opponent submits that the common factor of the patentee's arguments with respect to the documents cited on the ground of obviousness is the absence of ganciclovir, or monoesters of ganciclovir or amino acid esters of ganciclovir. It is submitted that the documents were placed under the ground of obviousness and the law of obviousness does not require the prior art document to teach exactly what is claimed in the concerned patent, that is the law of anticipation.**

**Notari et al does refer to hemi esters which are mono ester and it also refers to nucleoside analogues (page 49) The opponent cited Exhibit K of Stella Affidavit (Martin et al) wherein it was shown that both bis and mono esters have reduced activity. Thus, the opponent submits that there is no specific teaching that di-esters would work and mono ester would not, it is a matter of trial and error through which the skilled person verifies which ester has better function. There is always a likelihood of success and hence obvious to try with reasonable expectation of success.**

As for Beauchamp, 92 and 93 it is pointed out that the low oral bioavailability of ganciclovir lead the present inventors to develop the prodrugs to improve the bioavailability, so it is the so called problem to be solved which the inventors have alleged to have solved. Accordingly pointing to the same as disadvantage does not add any inventive feature or concept of "teaching away" which the patentee tried to show. As to the toxicity the opponent reiterates that the toxicity of valganciclovir is same as that of ganciclovir as evident from the product leaflet of the patentee itself. Accordingly there cannot be any inventive feature in the impugned patent.

Thus, the documents, are all relevant and motivates a person skilled in the art to arrive at the presently claimed compound as claimed in the impugned patent for reasons stated hereinabove. Thus the present patent completely lacks inventive step and is thus obvious to a person skilled in the art.

**12.2 The opponent pointed out that the opponent distinguished its Patent over Jensen et al by submitting that Jensen relates to ocular or parenteral compositions. The Ld.**

**Controller's attention was drawn to claims and page 25 and 26 of the impugned specification. The claims of the impugned patent does not relate to a specific oral routes. It is clearly mentioned at page 25 that the compound may be given as orally , systemically, parenterally, intra muscularly, intravenously, subcutaneously, intravitreally by an implant. It is evident from pages 25 and 26 of the impugned specification that the compound claimed can be administered through any route.**

12.3 The opponent submitted that the patentee did not make any submissions vis-à-vis crystalline form, even on the ground of S 3(d) although it cited a Mumbai Patent Office in the matter of application no. 413/MUM/2003, wherein the crystalline form of Clopidogrel besylate was patentable as it showed increased shelf life, i.e., stability and lesser toxicity.

12.4 The opponent submits that in the present matter the patentee did not even argue on the ground of nonpatentability under Section 3(d), but merely placed a decision whose facts are completely different from the present matter. It is submitted that the application under opposition as cited by the patentee was related to the crystalline form of clopidogrel besylate, whereas the present compound claims all forms not only crystalline. The application in the cited decision was found to be patentable on the basis of the data provided vis-à-vis the stability and low toxicity of the compound, no such data is available in the present patent and the toxicity/adverse effects are same as that of ganciclovir as mentioned hereinabove. Thus the cited case does not at all apply to the present facts and circumstances.

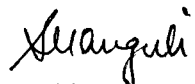
12.5 Regarding the Cipla and the Ranbaxy patent applications, the opponent cited that the portions pointed out by the patentee indicates that D6 of the present invention does not disclose the details of utility of mono ester or its preparation. It does not say that mono ester is not disclosed. As for enablement the opponent had made its arguments which the patentee did not even rebut and that the isolation of the monoester is conventional is already admitted in the specification of the impugned patent.

12.6 The Ranbaxy patent is for an amorphous form. In the prior art referring to D6 it does not mention that mono ester is not disclosed in the document. Accordingly the citation of these documents is baseless and does not add any weight in favour of the patentee.

Thus the opponent states that these documents are patent applications of Cipla and Ranbaxy and does not have any bearing to the present case.

In view of the above the patent may be revoked in toto as it is in breach of the various provisions of the Act as placed before the Ld. Controller with the written statement of opposition as well as at the hearing.

Dated this the 18<sup>th</sup> day of September, 2009

  
Dr. Sanchita Ganguli  
Of S. Majumdar & Co.  
Opponent's Agent

To

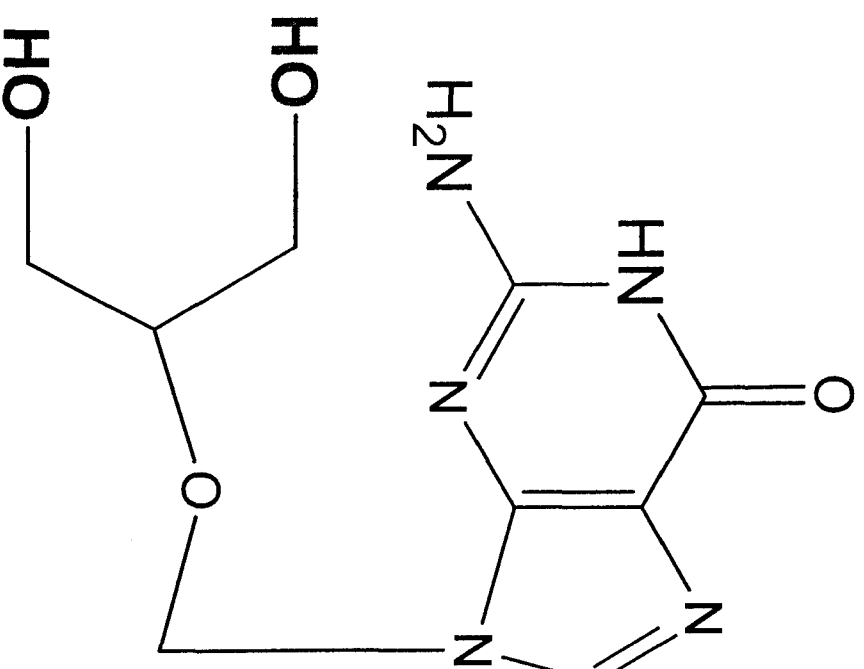
The Controller of Patents  
The Patent Office  
At Chennai

# Post Grant Opposition of

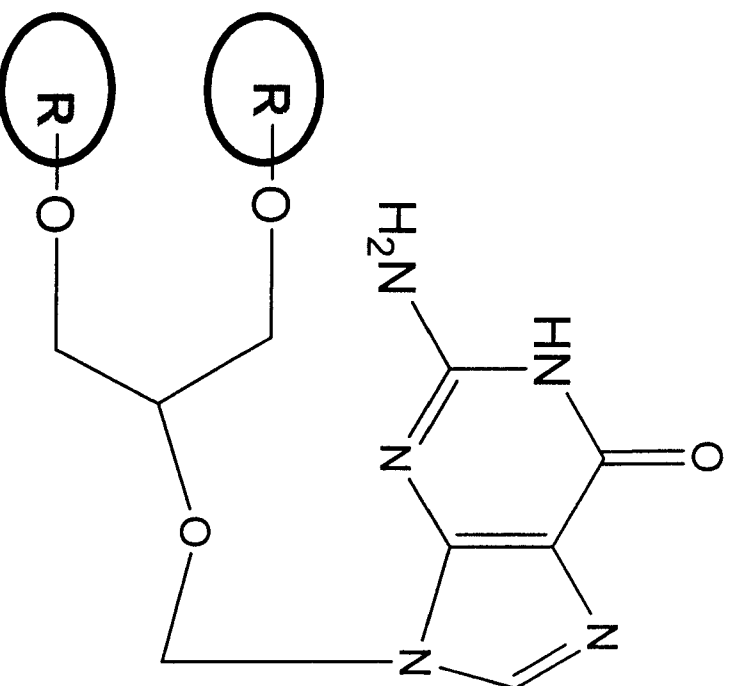
INDIAN PATENT NO:- IN207232

17/11/2017

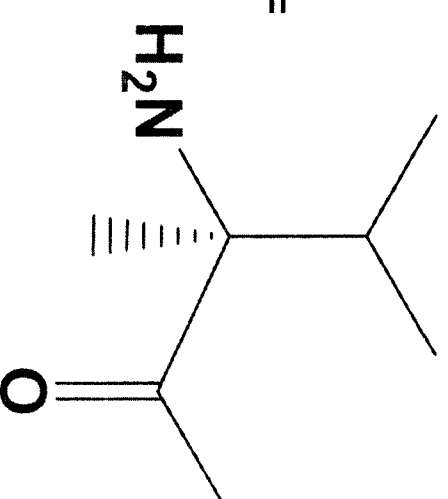
**Gancilcovir (admittedly known) disclosed in  
US 4355032**



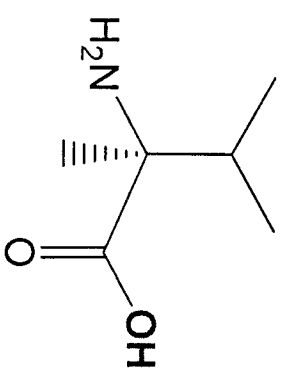
Bis L-valine ester of ganciclovir was disclosed in EP 375329 (D1) as prodrug with better bioavailability. Mono ester is also mentioned therein wherein any one 'R' in the below formula could be valine.



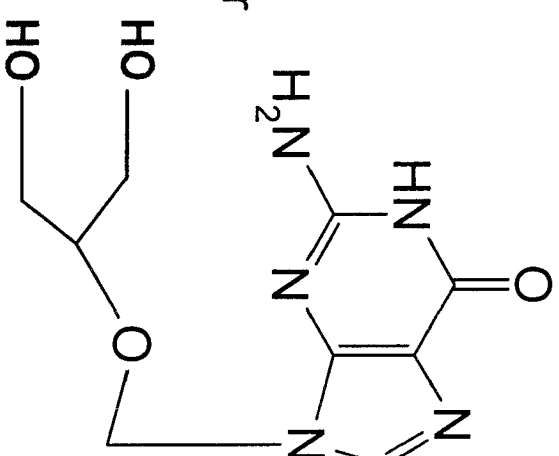
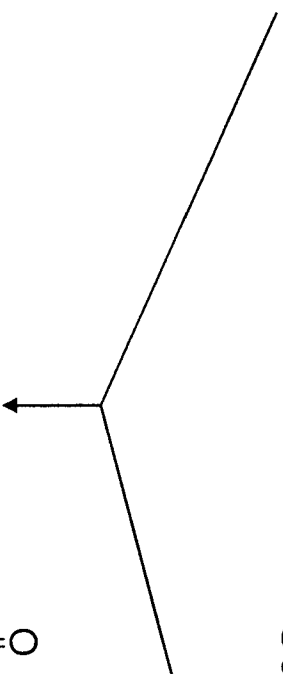
Wherein R =



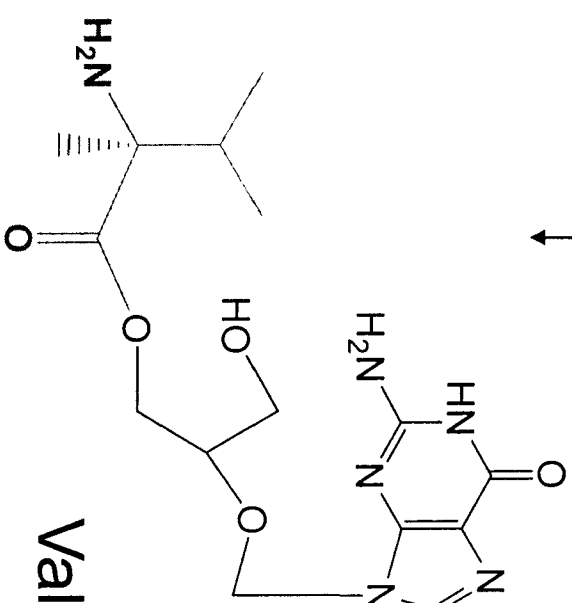
Valine



L-Valine



Ganciclovir



Valganciclovir

# Injectable Ganciclovir = Oral Valganciclovir

Dr. Ljungman says (page-14, point 48)  
“pharmacokinetic properties of valganciclovir  
is similar to intravenous ganciclovir  
than oral ganciclovir”

# Why was there a Need for Valganciclovir ?

## The need was to deliver ganciclovir Orally

Oral ganciclovir –Drawbacks,

- EP0375329 (acknowledged in the patent IN207232) stating ganciclovir has low oral bioavailability and is typically administered for 1 hour intravenously...every 12 hrs


- increase risk of ganciclovir resistance

Dr. Ljungman affidavit (para47)

- Limited oral bioavailability and the need for slow daily intravenous infusion of the drug...

IN207232 page-9 last para

# UNSUITABLE FOR ORAL USE

Ganciclovir (Drug)  Oral Administration

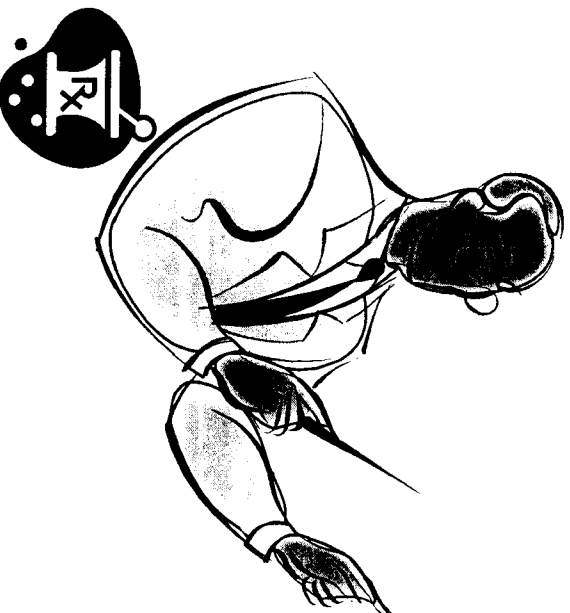


Ganciclovir reaches intestine



• In the process only 6-9% of the given dose is absorbed.

• Oral Ganciclovir gives about 1/8<sup>th</sup> activity of IV Ganciclovir



# Valcyte Roche (ER1) Page 2 “Mechanism of Action”

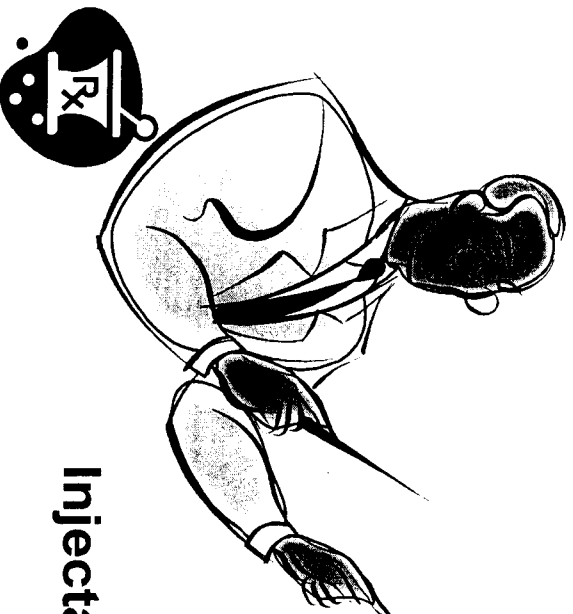
Ganciclovir  Valacyclovir  Oral Administration  
(Drug) (Prodrug)



Valganciclovir reaches intestine

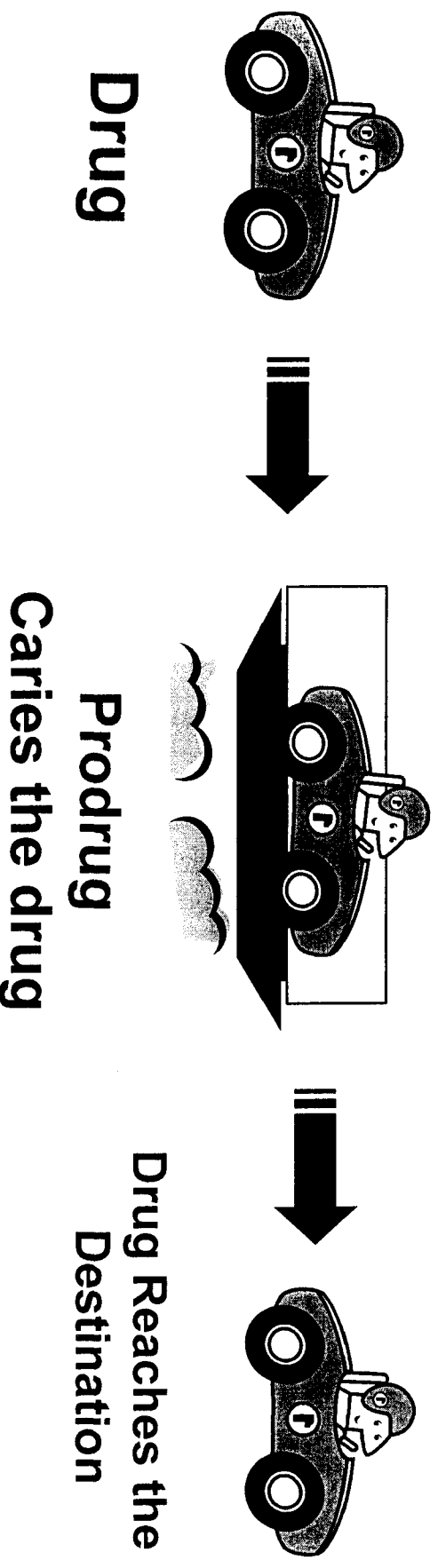


Rapidly converts to Ganciclovir  
by intestinal and hepatic esterases



**Injectable Ganciclovir = Oral Valganciclovir**

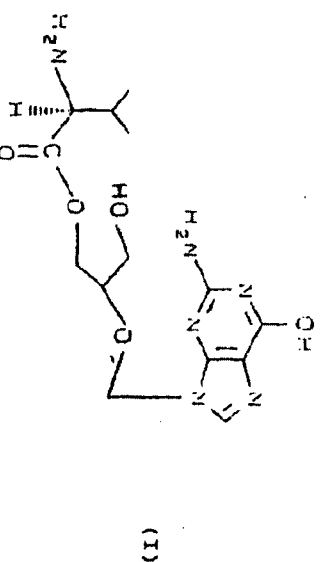
# Prodrug Design



Prodrug is an inactive compound formed intentionally linking a drug to an inert chemical by a covalent bond, which may be broken to yield drug itself in vivo

## Claim 1 of IN207232

A compound 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy-3-hydroxy-1-propanyl- L-valinate for the formula 1.



or a pharmaceutically acceptable salt thereof, in the form of its (R) of (S) diastereomers, or in the form of mixtures of the two diastereomer.

- Hydrolysis of a diester would lead to the formation of Chiral centre and hence lead to formation of enantiomer as given in prior art document Annexure 5 page 580

- In the present case the formation of enantiomers is inherent property of the compound there is no inventive step it is obvious from teaching of prior art

# Anticipation

Claimed compound is

2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl) methoxy-3-hydroxy-1-propanyl- L-valinate. (Valganciclovir).

- D1 contains disclosure of claimed compound (page 2 line 21-55 & page 3, lines 1-10) but patentee denies such disclosure (Reply statement para 11 & 22)
- D1 also teaches hydrochloride salt of claimed compound at page 3 line 9 also denied by patentee in reply statement page 16 para 24.
- R & S enantiomer would occur by default consequent on hydrolysis and is inherent.

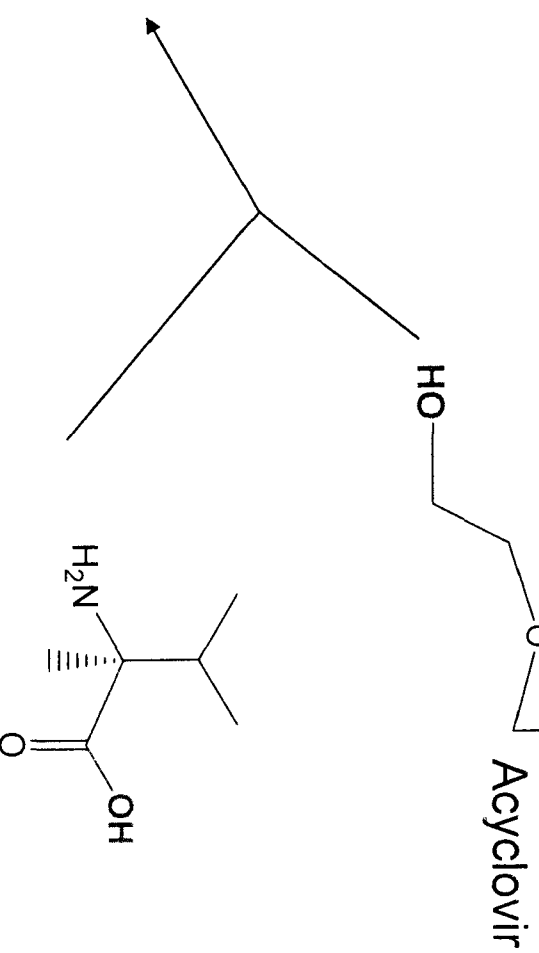
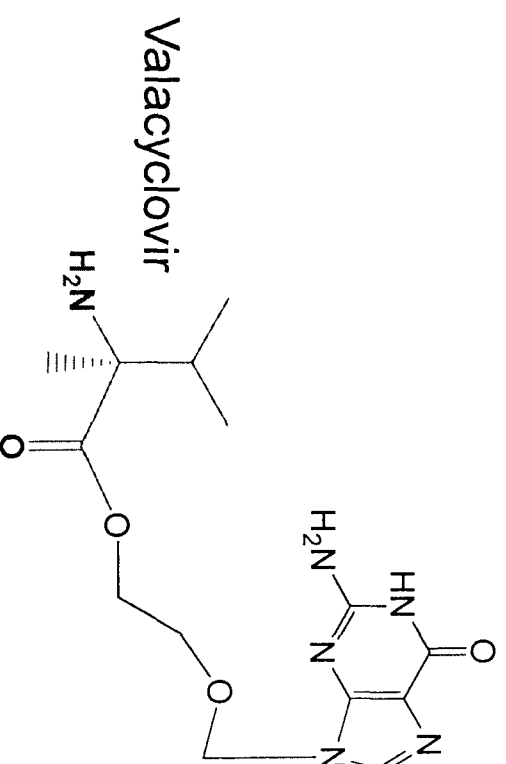
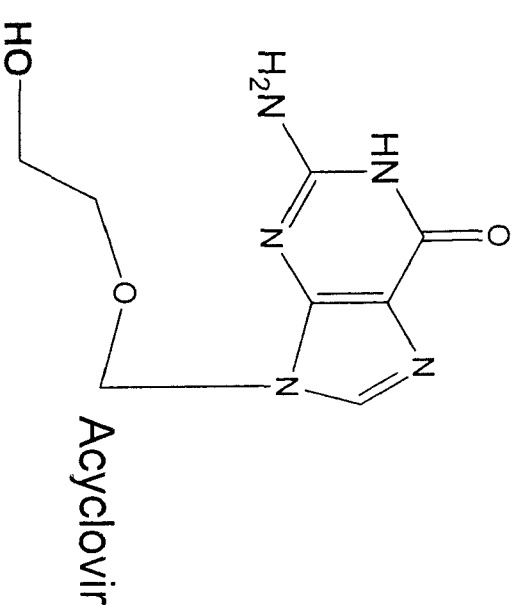
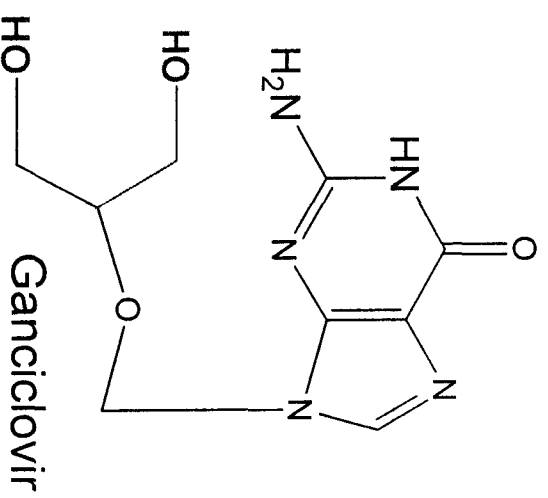
Thus there total disclosure in D1 of the claimed compound including its hydrochloride salt.

# Anticipation

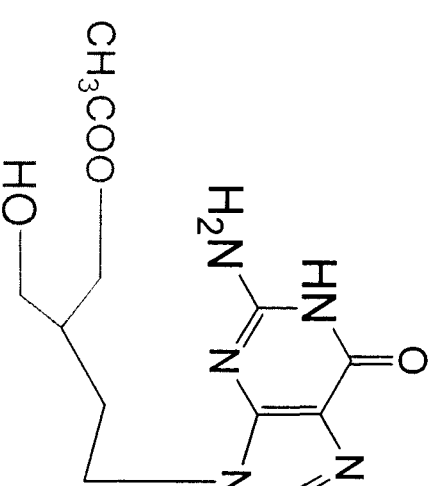
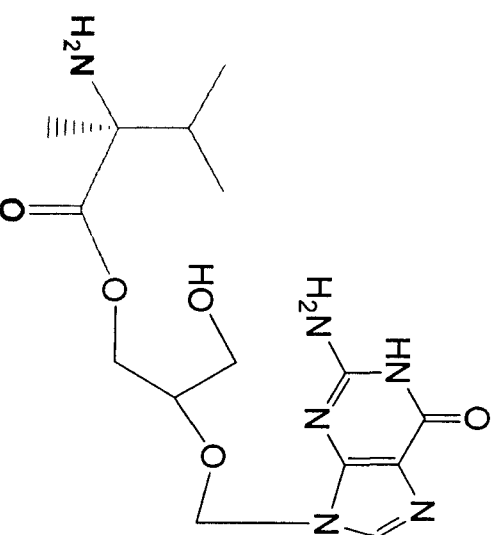
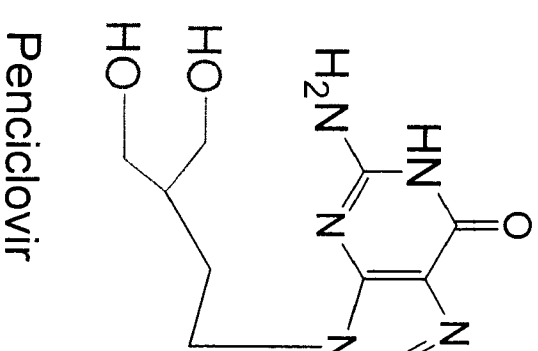
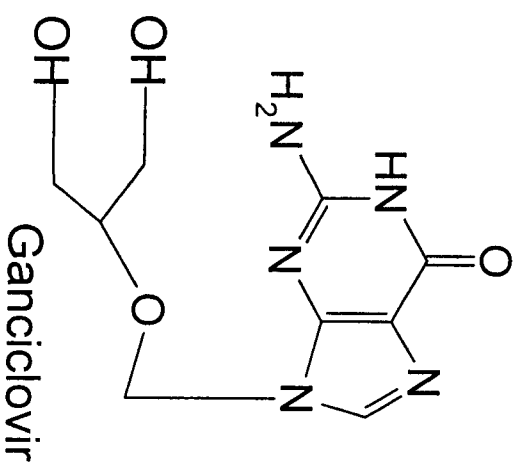
- There is total enablement in D1 for a skilled person prepared to display a reasonable degree of skill and use a common general knowledge in the art in making a routine trials and carry out ordinary method of trial and error which involve no inventive step and without carrying out any prolonged exercise of research enquiry or experiment

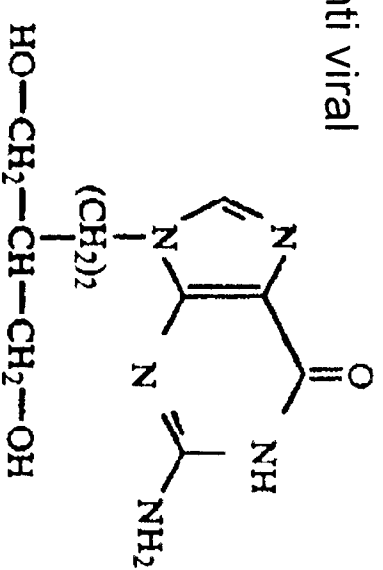
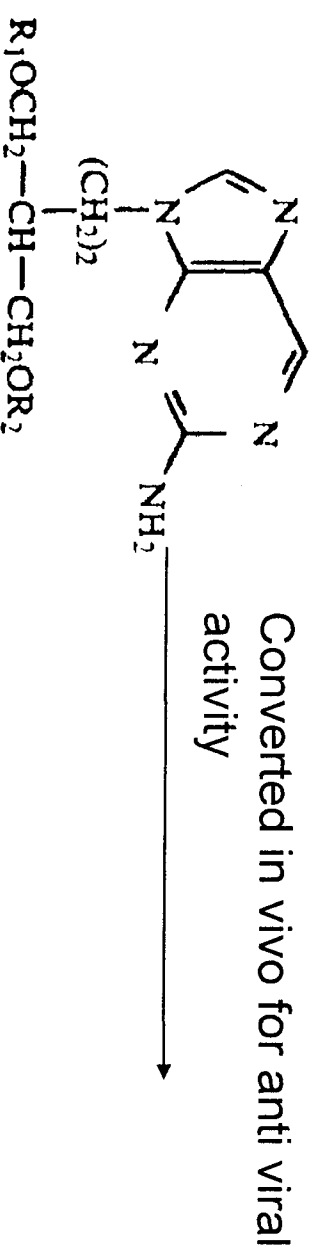
(2006 RPC 10)

# Obviousness



Beauchamp 92- D5 taught valine ester of acyclovir with best Bioavailability.  
Hence obvious to try.  
Acyclovir structurally close.  
Even EX Q of Stella Affidavit mentions that structural similarity provided impetus to try esters of Ganciclovir



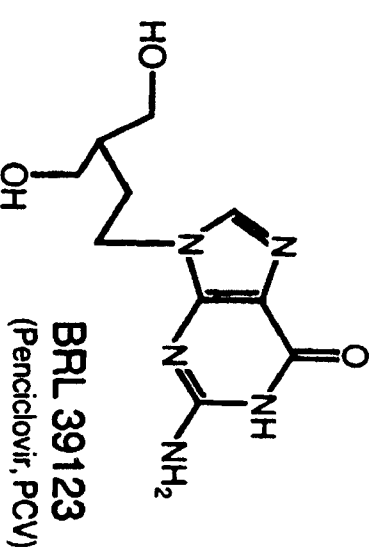
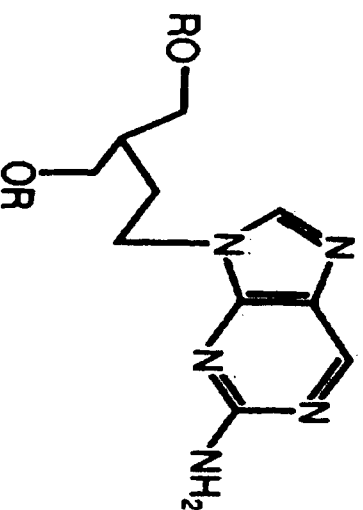


Penciclovir

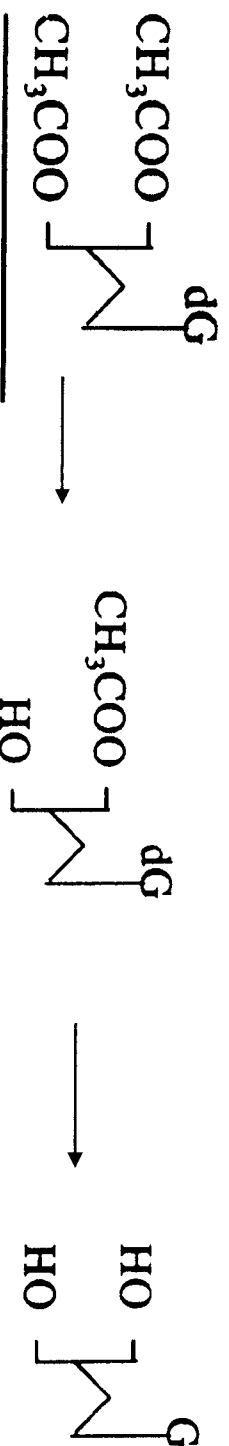
or a salt thereof, wherein  $\text{R}_1$  and  $\text{R}_2$  are each independently hydrogen, acyl or phosphate, provided that when one of  $\text{R}_1$  or  $\text{R}_2$  is phosphate, the other is hydrogen; or  $\text{R}_1$  and  $\text{R}_2$  are joined together to form a cyclic acetal group, a cyclic carbonate group or a cyclic phosphate group.

Examples of acyl groups for  $\text{R}_1$  and  $\text{R}_2$  are those where the group  $\text{R}_1\text{O---}$  or  $\text{R}_2\text{O---}$  is a pharmaceutically acceptable ester group, such as a carboxylic ester group.

In the case of compounds of formula (I) wherein one of  $\text{R}_1$  or  $\text{R}_2$  is an acyl or phosphate group, the compound exists in two enantiomeric forms. The invention includes both enantiomers in isolated form and mixtures thereof.



**BRL 42359**      **R = H**  
**BRL 42810**      **R = CH<sub>3</sub>CO**  
 (Famciclovir, FCV)  
**BRL 43555**      **D - L L L L L**



Famciclovir

Monocetyl ester

Penciclovir

Exhibit 9 of opponent teaches Famciclovir developed to increase oral bioavailability is first hydrolysed to monoester and then to Penciclovir. Hence it is obvious if this salt is known it would hydrolyse to mono ester before forming the drug. Monoester of penciclovir also taught in US'688 which has enantiomeric forms, crystallinity, forms salts- hydrochlorides

# Section 3(d)