

# **The Patents Act, 1970**

## **Section 25(1)**

In the matter of Application  
for patent no 3598/ DELNP/ 2004

And

In the matter of representation  
under section 25(1) of the Patent  
Act, 1970 as amended by Patent  
(Amendment) Act, 2005.

And

In the matter of rule 55 of the  
Patent Rules, 2003, as amended by  
the Patent (Amendment) Rules, 2005.

M/s Tibotec Pharmaceuticals Ltd, Ireland ... The Applicant

M/s Cipla Ltd Limited., India ... The Opponent

## **Hearing held on 13<sup>th</sup> March,2009**

Present

Mrs. Rajeswari ... Agent for the opponent

M/s Gowree Gokhale

Sh. S. Majumdar ... Agent for the opponent

## DECISION

A representation by way of opposition under section 25(1) of the Patent Act as amended by Patent (Amendment) Act 2005 was filed by Cipla Limited, with a request for hearing under rule 55 of the Patent Rules 2003 as amended by Patents (Amendment) Rules 2005. The applicant accordingly submitted their reply statement and evidence on September 30, 2008.

The present application was filed by M/s Tibotec Pharmaceuticals Ltd, Ireland, which is a national phase application of PCT/ EP03 /50176 claiming priority of EP02076929.5 dated 16/05/2002. This application was filed on May 16, 2004 for an invention claiming "Pseudo polymorphic forms of a HIV Protease Inhibitor", was allotted the application number 3598 / DELNP/ 2004.

Here it is pertinent to note that the hearing was fixed on December 12, 2008 and both the parties to the opposition attended the hearing on the scheduled date. But the applicant filed their expert evidence along with amended claims on 12<sup>th</sup> December, 2008 after filing the reply statement on Sept. 30, 2008. The opponent in view of the applicant's submission, pleaded to allow a new document, to reply the reply statement of the applicant, to take on record. This was objected to by the applicant. Also the evidence and the amended claims were sent just seven days before the date of hearing and the opponent pleaded that they received incomplete documents and rest of the documents received on the eve of hearing, which they could not study. Opponent pleaded for adjournment of the hearing to facilitate to file replication in view of above document filed by the applicant. The applicant also replied that in case the fresh document of the opponent is taken on record they need time to reply the said opponent's reply. The hearing was therefore adjourned in the interest of both the parties and the opponent was allowed to file replication by earliest and applicant to submit reply on the said replication. On receipt of reply from both the parties fresh date of hearing was fixed on 13<sup>th</sup> March, 2009 and both the parties attended the hearing.

The opponent filed their written statement of opposition on the grounds of (1) Insufficiency of description (2) Obviousness / lack of inventive step (3) Anticipation (4) Not an invention /not patentable and (5) u/s section 8. However with the submission of the amendment in the claims by the applicant the opponent opposed on the following three grounds only;

(1) Obviousness / Lack of inventive step

(2) Not an invention / Not patentable

(3) Insufficiency of description

The opponent argued that the originally filed claims of the impugned application related to pseudopolymorphs, of compound 'x' namely 'DARUNAVIR' and the process of preparing these pseudopolymorphs. According to page 3 line 13-14 these pseudopolymorphs have improved bioavailability and stability. however applicant amended the claims and claimed only two specific pseudopolymorphs the ethanolate and the hydrate forms and their respective process of preparation .The expert evidence submitted that such improved stability and bioavailability is peculiar to this compound over prior art. The opponent also argued against the reply statement of the applicant wherein it pleaded that "the opposition is not maintainable as the opponent failed to file any evidence". The opponent submitted that the prior art document submitted with the representation , serve as the documentary evidence and relied on the decision of Indian Patent Office in the case of F.Hoffman-la Roche ltd Vs Wockhardt Limited. Therefore the prior art evidence is also an evidence and ought to be considered for the purpose.

In respect of the ground of **Obviousness /lack of inventiveness** the opponent relied upon WO 99/67417 (D1), filed with the representation submission .Later the document US 6287693 (exhibit-A) , US 6098779 (exhibit-B) ,polymorphism in pharmaceutical solids (exhibit-C) and the office action dated Oct 22,2008 (exhibit-AA) of the US counterpart of the impugned application, which was filed along with replication of the opponent.

With respect to D1 , the opponent submitted that WO99 /67417 published on December 29, 1999 teaches the base compound 'X' whose pseudo

polymorphs with alleged improvements in bioavailability and stability have been claimed in the impugned application .Specifically fig 5A and first compound in the Table-4 on page 81 of D1 teaches the compound 'X' is used in the treatment of HIV, example 11 on page 79, line 20-22 reads as “compound 32 and the analogs thereof are predicted to be potent in preventing the selection of these viral strains in vivo” and example 18, which teaches the compound 35 of fig 5A i.e. compound 'X' , has inhibitory activity .

The opponent argued that exhibit A i.e. US 6287693 dated September 11, 2001 related to storage stable particles of allotropic compounds. Exhibit A teaches that crystallization is induced to increase the stability of therapeutic compounds .It also teaches vide column 2 that hydrates are sometimes most stable polymorphs of therapeutic compounds . “some workers have attempted to improve the stability of the therapeutic compound by inducing crystallization . For instance Mastuda et al suggest modifying the crystal structure using a temperature controlled dispersion drying method – ***Mastuda et al physico chemical characterization of sprayed dried phenyl butazone polymorph***” ,***J,Pharm. Science,Vol 73 ,No.2 , 73-179 (1984)*** “. Column 3 of the same document, line 21 states “the method of the present invention afford several advantages. It is applicable to substances where the most stable polymorph is a hydrate, because it does not drive off water molecules and thereby allows the incorporation of the water molecule into the crystalline web during formation.

Column 4 ,line 22 it states “The solvent or solvents used in the method of the present invention can be any agent classified as solvent for the organic compound(s) of interest , as will be appreciated by any ordinary skilled worker in the art, the solution of solvent will depend on the compound(s) sought to be stabilized. Exemplary solvents are conventional laboratory liquid solvents such as water, alkenes, alcohol, ketone , aldehyde ,ether , ester , various acids including mineral acids etc.. Some specific solvents are ethanol, methanol, propanol, acetone, hydrochloric acid, THF, ethers, pentane ,hexane, xylene, benzene. Water is especially useful component of a solvent / liquid mixture of the

present invention, particularly where the most stable polymorph of a substance is a hydrate,”

Column 5 , line 49 states , “ ***the combination of the uniformity of the size and shape of the particle and the uniformity and stability of the crystalline structure of the constituent organic compound lends particular predictability and consistent bioavailability and associated bio dynamics***”.

The same document further clarifies the term crystallization and recrystallization – “crystallization refers to a process by which the most stable polymorphs of a particular substance is achieved. Recrystallization refers to a process similar to crystallization except that the organic compound of a particle rather than being amorphous was initially only partially crystalline of a mixed crystalline habit, or crystalline but of a less stable crystalline form “ .The same document vide example 1 demonstrate the higher stability of the hydrate form .

Therefore, the opponent argued, that the D1 and the exhibit read together clearly motivates a person to try to formulate polymorphs and pseudo polymorphs with solvent molecule incorporated into there crystal lattice, in order to obtain therapeutic compound with enhanced bio availability and stability. The opponent argued that in the light of the above, the solvates (ethanolate and hydrate) of the impugned invention are obvious and lack in inventiveness.

The opponent placed another prior art document exhibit B i.e. US 6096779 dated August 1,2000 which also teaches the improved physicochemical properties of the polymorph over the base compounds. Column 1,line 29 of the exhibit states , “**for improving the slight solubility of Piretanide form A in an acidic environment ,it has been suggested that a piretanide polymorph obtained by crystallizing a piretanide from a lower aliphatic alcohol or a cyclic ether to form a crystalline solvate and then heating the resultant solvate provide piretanide form B**

- {*Japanese Patent Kokoi No. 230044 /1993 and chem.. pharma Bull,(1994) vol 42, page 1123-28* } .Piretanide form B has a solubility of 12.4 mg/ml and 6.4 mg/ml at 37 degree centigrade in a buffer at a pH of 1 and 3 respectively and its solubility in an acidic environment increased by a factor of 1.5 to 1.7 than the

piretanide form A. In view of pH value of 'one' in gastric juice, piretanide form B which has a crystalline form more suitable for oral administration ". . . . . ."The solvent which are employed in this invention includes water, and an aqueous organic solvents such as aqueous alcohol e.g. aqueous methanol, aqueous ethanol etc .the aqueous solution of base such as sodium hydroxide ,potassium hydroxide etc" .

Therefore exhibit B teaches that to increase the solubility of paretanide ,the compound was crystallized to form a polymorph. The superior solubility of the polymorph namely the hydrate was demonstrated by way of an example. The opponent argued that, from this document it is amply clear that polymorph or solvates have enhanced solubility compared to base forms .Which is a clear motivation to try polymorph of compounds to obtain the desired superior solubility. A person ordinarily skilled in the art on reading D1 and exhibit B would be motivated to try the polymorph of the base compound in expectation of better physico- chemical properties like stability, solubility and bio availability to make it more suitable for oral administration.

The opponent placed another document exhibit C i.e. "Polymorphism in Pharmaceutical solids" is a 1999 publication. The publication teaches that the solvates or pseudo polymorphs are known to increase the stability of the compounds and even the ratio of the compounds to the solvent which is generally 1:1 water and alcohol. These solvents are present in the commonly used solvents as disclosed in table 2 page 206 of exhibit C. Therefore a person ordinarily skilled can have very clear understanding of polymorphism by what has been taught in these publications. It is to be noted that 1:1 ratio of water to ethanol is the only enabling example available in the impugned application. The opponent argued that the invention is therefore not only devoid of all the inventive features but also lack in any unexpected or surprising increase in stability, solubility and bio availability.

On the basis of the above, the opponent argued that it is clear from the teaching of the exhibit A, exhibit B and exhibit C which clearly teaches that the solvates and hydrates of the base compound provide greater stability and bio availability

and which clearly motivates a person to try out polymorphs (solvate ,hydrate) of the compound with reasonable expectation of success in achieving superior physico- chemical properties. The compound 'X' was known and its polymorphs are already known, the applicant only provided the pseudo polymorphs of compound 'X' having improved solubility and stability, which is quite expected as provided in exhibits A,B and C. Accordingly the impugned invention is obvious and devoid of inventive step.

The opponent also submitted that at paragraph 10.9 of the reply statement the applicant has stated and in Joel's affidavit ,the expert has reiterated that the table 7-9.12-17,19-21,24-26 in the specification show the improved stability and the solubility of the ethanolate and hydrate over the amorphous base compound 'X'. The opponent asserted that none of the table show comparison with the amorphous base compound . The applicant also gave the misleading statement that example 24 form A shows improved safety, tolerability and pharmacokinetics as compared to the amorphous base compound 'X'.

The opponent also argued that in the Han's affidavit, it has stated that there is no indication ,teaching or suggestion in the D1 that a solvates would have been formed. The expert has completely failed to construe obviousness as indication , teaching or suggestion need not be present in the same document and may even be available as common general knowledge to a person skilled in the art. In the present case the exhibit A,B &C were all available before the priority date of the impugned application and all these clearly indicate , teach or motivate a person skilled in the art to prepare polymorph of compound with reasonable expectation of success for achieving better properties.

The opponent drawn the attention, that the paragraph 28 & 29 of the Joel's affidavit, the expert has stated that polymorphs are often preferred to amorphous form as they exhibit higher stability and there is an expectation, polymorphs are obvious to try but again there is no guarantee of success. The expert states **"..... that stability is expected on polymorphism but the solubility and bioavailability of a compound decreases on polymorph formation and since in the present case , stability ,solubility and**

***bioavailability has increased , the same is non-obvious over the prior art “.***

To this the opponent argued that ,exhibit A teaches that both bioavailability and stability of a polymorph is expected to be better than the base compound , exhibit B teaches that the solubility of a polymorphs are much more than the base compound and the same has been corroborated with an example. Therefore considering exhibit A and B, it becomes evident that polymorphs have better stability , bioavailability and solubility than the base form .Thus it is obvious to formulate pseudopolymorphs (hydrate ,solvate) of the compound ‘X’ to achieve better stability , solubility and bioavailability if any , given the teachings of exhibit A and B .

During the hearing applicant relied upon Dr. Hans’ affidavit vide schedule 1, to show the bioavailability of ethanolate pseudopolymorphs specially the AUC values compared to amorphous values . The opponent argued that the AUC values vide table TK3 on page 3/6 and 5/6 has increased by 300% to 400% but the comparison is between capsule dosage and not a tablet. Table TK3 at page 3/6 represent the individual and mean pharmacokinetics parameters which varies enormously from one animal to another animal ranging between 201 , 826 and 4058 ng.h/ml for treatment C in TK3 for tablet form , treatment A at page 1/6 the same parameter varies with values 5086 , 16567 and 9810 ng.h/ml . The opponent argued that if for the same treatment the result could vary in such an erratic manner for three animals, any researcher would have taken more animal to substantiate the data and would not based any conclusion for such erratic data. The opponent submitted that such data is highly fluctuating and no way such efficiency can be extrapolated to humans. The applicant during hearing also relied upon the bioavailability data, wherein the comparison was made between treatment C (capsule of ethanolate form of compound ‘X’ ) and treatment E (amorphous form of compound ‘X’ ) to show the unexpected increase in bioavailability. The opponent submitted that the applicant deliberately compared treatment C with treatment E leaving out treatment A which pertains to tablet dosage form of form A of compound ‘X’ . It is to be noted that on interpreting the corresponding graphs it is evident that the bioavailability of the

tablet form (treatment A ) follow the same trend as in treatment E i.e. in amorphous form . Therefore unlike the applicant's claim , the unexpected bioavailability data support only the capsule dosage form (treatment C )of the form A while the data of treatment A is in line with amorphous form . However treatment data shows an unusual variation with in three animal as well as increase in plasma concentration from 4 to 7<sup>th</sup> hour . Therefore the data relied upon by the applicant provides erratic results whose mean values are also erratic. Therefore the data does not prove any point leave alone showing any inventive step. Also the test data submitted by the applicant vide schedule 1 of the Hans' affidavit are all with respect to ethanolate form and no data has been provided to corroborate the finding with respect to hydrate form.

In the Dr. Hans' affidavit vide paragraph 8 , it states that substantial time, investment and experiments have been undertaken to determine the method for obtaining solvates . The opponent pleaded that the patent can not be granted merely on the basis of the fact that much time and investigation were made relating to the compounds, it should have inventive ingenuity to be patentable. Therefore the pseudopolymorphs 1 to 11 are not only obvious to try in the light of the prior art dealt with it but also there was a reasonable expectation that properties like stability, solubility and bioavailability would be substantially enhanced.

The opponent in support of their pleading for obviousness gave some case laws .

**(1) EPO Board of Appeal Decision , T0051 /97-3.3.1 date of decision 24<sup>th</sup> August ,2000**

**“.....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 and 3 above, namely, by transforming the modification of the azo dye of the formula 1 known from the closest prior art document (cf point 2.2 above ) into the modification thereof , thereby arriving at the solution proposed by the patent in suit. In the Board's**

***judgment, 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.***

***Therefore in the Board's judgment, the subject matter of claim 1 represent an obvious solution to the problem underlying the patent in suit and does not involve an inventive step .....***"

The opponent argued that according to the previous paragraph a person skilled in the art would get concrete hint from document of prior art trying to solve the same problem . In the present case the applicant have found that the pseudopolymorphs have so called improved stability. And bioavailability over the base compound. Citation A and B are relevant document as both relates to therapeutic compounds, which would provide a concrete hint to try pseudopolymorphs (solvate and hydrate ) for improve physico chemical properties. Following the same analogy as in the decision , the impugned application is obvious to try with reasonable expectation of success.

***(2) EPO Board of Appeal decision , case no. T0200/05-3.3.10 date of decision June , 2008***

***".....furthermore when assessing inventive step it is not necessary to establish that the success of an envisaged solution of a technical problem was predictable with certainty. In order to render a solution obvious , it is sufficient to establish that the skilled person would have followed the teaching of the prior art with a reasonable expectation of success.....***

***in the present case ,the board could not agree with the respondent's argument that due to some purported uncertainty about the predictability of success , the skilled person would not have contemplated using a polyhydric alcohol as solvent .....Board could reasonably conclude that the skilled person would have been deterred from following straight teaching of the art. In the absence of substantiating facts and***

***corroborating evidence the respondent's argument do not convince the Board "***

The opponent argued that the above said case , the decision clearly stated that the teaching of a probable solution ,even if the solution is not certain, reasonable expectation of success rules out any inventive step involved in the invention . In the present case prior art exhibit A,B and C were available which clearly teaches that polymorphs (solvate ,hydrate) exhibit better physicochemical characteristics .The prior art even discloses the commonly used solvents which includes ethanol and water , used in the impugned application. The exhibit C teaches the preferable ratio of the compound to solvent 1:1 which is the same used in the only enabling example is provided in the impugned application. Therefore impugned application is rendered obvious and lacking in inventive step.

***(3) case law Pfizer Inc Vs Apotex Inc. (United States Court of Appeal for the federal circuit 2006 1261 )***

In this case the district court found that the skilled artisan would have had no expectation of success in making a basylate 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 . The Appeal Court said “ ***...the problem with the District Court's ultimate conclusion of non obviousness based on that factual finding, however is that the case law is clear that obviousness can not be avoided simply by showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. But once again only a reasonable expectation of success is 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 Sanofi- synthelabo Vs Apotex Inc. 470 F3d, 1368,1379,Fed. Circuit 2006). The mere possibility that some salt may not form, does not demand a conclusion that, those that do are necessarily non-obvious. This is specially 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 . Second this is not the case where prior art teaches merely to pursue a general approach that seem to be a promising field of expectation 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 as 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 “ .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 skilled in the art that the process should be carried out and would have a reasonable likelihood of success (Merck 874, F.2d at 809 – quoting in re. Dow chemical company 837 F.2d 469, 473 fed cir 1988 ) For this reason we hold that Apotex introduced clear and convincing evidence that a skilled person would have had reasonable expectation of success with the besylate salt form of amlodipine at the time invention was made. Accordingly we agree with District Court that a prime facie case of obviousness was established with regard to claims of '303 patent .*

Mr. Joel the expert vide Para 28 himself stated that *though it may have been obvious to try to crystallize amorphous material (compound X ) it was by no means obvious that such efforts will be successful .* As per the expert knowledge, making a pseudo polymorph in expectation of better physico chemical properties viz. Stability is obvious to try, what is expected is the actual increase in such properties. According to Pfizer V Apotex as well as T0200/05-3.3.10 mentioned above, a reasonable expectation of success is enough to negate patentability. The opponent argued that the applicant has carried out the

invention with a reasonable expectation of success and achieve the result which is expected /desired and nothing non-obvious or surprising. The applicant has not shown evidence to support the unexpected increase in the efficacy of the pseudo polymorphs as discussed above and accordingly impugned invention is obvious.

In respect of **Not an invention /not patentable** the opponent submitted that as the impugned application lacks inventive step under section 2 (1) ( ja ) vis-a vis document cited to determine obviousness . As the patent fall short of an inventive step, it is not an invention u/s 2 (1)( j) of the Act and hence not patentable .

The opponent also submitted that the present application is **not patentable** u/s 3(d) as the applicant failed to show the enhanced efficacy as claimed with respect to the base compound known in the prior art in support the opponent refer to the case **-High Court of Madras, WP no. 24759 of 2006, Novartis Vs Union of India & ors (along with WP no.24760 of 2006)** and drawn the attention of the tribunal that ***the therapeutic efficacy 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 application 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. “ Thus it is evident that efficacy is to produce desired therapeutic effect and therapeutic effect is healing of disease .. Therefore in order to show the enhanced efficacy as required by the section 3 (d) is to demonstrate improvement in efficacy in terms of therapeutic effect of healing a disease.*** However the applicant has failed to show any such enhanced efficacy as required by the act and defined by the hon’ble high Court of Madras.

The opponent argued that the applicant should have shown how and whether the pseudo polymorph of the impugned invention has any enhanced healing effect in terms of treating HIV infection compared to that of the amorphous compound ‘X’ . A medicament is available to the system when the

substance dissolves . It is immaterial for the purpose of efficacy as to how quickly or slowly the substance has dissolved . Different physical forms of the product may have different physical properties giving differing degree of stability, solubility and bio availability does not effect the properties of the drug .If a given form dissolves fast the action is quicker as compared to slow dissolution and consequently lower bioavailability but that can not make the character of the drug different. A proper comparison of efficacy would have been a comparative therapeutic profile of the drug when administered parenterally vs. in the form of pseudo polymorph vs. amorphous form .In such a comparative study efficacy could be claimed if the polymorph showed therapeutic profile of the drug which is higher comparative to parenterally administered route. In other words even if the alleged improved bio available pseudo polymorph of the impugned invention were available at the site of action of same time with the parental form, it needs to be shown that the pseudo polymorphs (etanolate, hydrate ) brought down the HIV infection to a greater extent or caused a greater level of HIV protease inhibition than the parental form. Any thing short of the same can not be regarded enhanced efficacy to qualify as an invention under Section 3(d) .

There is no data to show efficacy of any of the pseudo polymorphs on alleviating HIV infection There is no data to show efficacy leave alone enhanced efficacy of the pseudo polymorphs over the known compound 'X' . Improved stability and bio availability can not be equated with enhanced efficacy .Han's affidavit only teaches that the ethanolate form of the compound 'X' when used with low dose of 'ritonavir' shows greater efficacy than other protease inhibitors, which is a mere statement as there is no data provided and also it is not clear whether the protease inhibitor activity is due to 'ritonavir' or the 'ethanolate form'. Even to show potency as construed by the applicant (Joel's statement referring Merck Manual that the drug effect is mentioned to be evaluated as potency or efficacy ) there needs to be shown that with a small amount of pseudo polymorphs greater control of HIV infection is attained. Accordingly it is stated that there is no enhancement of efficacy in the action of pseudo polymorphs compared to that of the amorphous compound 'X' of D1 and hence both are to be

construed as the same substance according to Section 3(d). Hence it is stated that the impugned invention ought to be rejected under Section 3(d) .

In respect of **insufficiency of description** , the opponent submitted that all the range of ratio claimed has not been enabled in the description and only 1:1 ratio has been enabled by way of example -1 , accordingly claim 2,3 and 4 ought to be rejected.. Claim -7 that is drawn towards a process of preparation of ethanolate pseudo polymorph (form A) of compound 'X' is in fructuous as it is totally inconsistent with that of example-1 of the specification . In the example form A is prepared from the isopropionate form of the compound 'X' and not by combining compound 'X' and ethanol or ethanol and water mixture as allegedly claimed in claim -7. Claim-8 made dependent upon claim -7 though not at all dependent. Claim-7 provides preparation of form A by combining compound 'X' with ethanol or ethanol and water whereas claim-8 claims something quite outside claim-7. Claim-8 provides preparation of form A from isopropanolate form of compound 'X'. Further claim -11 draws towards the hydrate form (form B) ,for which no supporting data for stability or bioavailability etc has been provided. In the reply statement the applicant has stated that the preparation of form B is exemplified by way of example -2 of the specification which is completely a false statement. Example-2 pertains to preparation of form B and form D and not form B per se. Therefore claim -11 should be rejected with claim 12 to 15 for insufficiency of disclosure. Even in the expert opinion ,the data submitted during hearing proceedings , no data relating to hydrate form has been provided. Therefore applicant has completely failed to discharge the duty of sufficiency of description of the invention and the impugned application be rejected on the ground of insufficiency of disclosure.

The opponent concluded after the above arguments on the three grounds taken by them. The applicant submitted its own argument against these grounds.

The applicant stated that U/s 25(1) (e) 'the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step....."The word clearly has been inserted in section 25 with a

purpose i.e. for the purpose of an pre-grant opposition ,the test for obviousness is quite high and invention has to be obvious beyond reasonable doubt. If the controller has the slightest doubt then he has to give the applicant the benefit of doubt. Also the burden of proof lies with the opposition to prove the case on obviousness beyond reasonable doubt. The applicant submitted that the opponent has miserably failed to discharge the burden.

The applicant argued that it is generally known in the art that amorphous form are unstable but more soluble and crystalline form are more stable but has reduced solubility than amorphous form. In the present invention though crystalline form provides higher bio availability than that of amorphous form. In view of the above it would be an obvious to person skilled in the art that the crystalline form of the compound 'x' would have higher bio availability than the amorphous form . This fact is clearly mentioned in the affidavit of Joel Bernstein “.....***The appearance of all the solvates ,their composition and their properties in the application could not be predicted in advance. The fact that the crystalline forms may result, may not be a surprise but which crystalline form and the properties of that crystal form are a surprise to be revealed only when crystalline form is characterized.*** As noted above when the crystal form is prepared from amorphous solid one generally expects improved stability but lower solubility. Difference in bioavailability are related to solubility and dissolution, but are much more difficult to predict, especially on a qualitative basis. The claimed form (form A, form B )advantageously overcome this compromise and provide enhanced bioavailability and stability.”

The applicant argued that the opponent has acknowledged in Para 5 of the representation that inventive step is assessed by establishing the closest prior art, determining the technical problem to be solved and thereafter to assess the claimed solution to the problem in view of the prior art. The present invention solved by way of claimed invention by providing pseudo polymorphic form of compound 'X' having improved stability and enhanced bioavailability .

The allegation of the opponent that specification does not provide the characteristic data comparing stability and bioavailability of the claimed form vis-

à-vis compound 'X', but such data are available in the specification vide table 7-9 and table 12-17 for solubility and stability of form A and table -19-21 for solubility and stability of form B. Further crystalline forms are known to be more stable than the amorphous forms and data with regard to enhanced bioavailability is provided in schedule to Han's statement.

With respect to the opponent's claim that "*the subject application are obvious in view of D1 read with US 6287,693 , D1 read with US 6096,779 and exhibit C of the replication . The opponent submitted that D1 discloses the compound of formula 'X'. US '693, US '779 and exhibit C teaches preparation of amorphous/solvates/crystalline forms and that the disclosed method are conventional method and there is nothing novel or inventive about making such an ethanolate or hydrate "*, the applicant argued that the prior art D1 cited by the opponent does not even remotely relates to or relevant to the invention in question . D1 is a patent for fitness assay , which can be used to predict the biological fitness of a mutant under selective presence of an inhibitor of a biochemical target . The invention does not relates to or teach the use of pseudo polymorphs in the management of HIV, let alone the compound 'X'. Its aim is to determine the biochemical fitness in the presence of drug. The only mention of the compound 'X' occurs in fig -5A which is shown as one of the several compounds that were tested against various drug resistant HIV mutants. The applicant also argued that the relevance of example-11 to preparation of solvates is wrong as it is related to the preparation of HIV inhibitor of formula -32 whereas the compound 'X' is represented to figure -5A as compound -35. There is no indication of any process step for obtaining a compound of formula 'X'.

The document US '693 relates to a process of preparing stable crystalline organic compounds by exposing the organic compound by solvent vapour. The process is no way connected to ethanolate form. The opponent relied upon 6<sup>th</sup> paragraph of column of US '693 "**...The combination of the uniformity of the size and shape of a particle and uniformity and stability of the crystalline structure of the constituent organic compound lend particular predictability and consistent bioavailability**". The applicant said that opponent are purposely

misinterpreting the said specification. The above said Para can not be interpreted to mean that the crystalline form have predictable high bioavailability.

The document US '779 is a patent for novel amorphous piretanide, a novel class of piretanide, a novel class of Piretanide polymorphs and their method of preparation. The entire process is described on column -2 which involves dissolving Piretanide in aqueous solution of a base, adjusting pH value and recovering the precipitate etc. It is to be noted that at the priority date of US '779 which was 1996, polymorphs and their methods were known, yet the patent was found novel. In the US '779 there is no general teaching direct or implied, this prior art in no way provide a general teaching that solvates produced have higher solubility and bioavailability. Thus none of the prior art relied upon by the opponent teaches a process whereby ethanolate solvate crystal having higher bioavailability may be prepared.

With respect to the opponent submission that *“prior art generally teaches the compound ‘X’, general method for preparation of crystal and solvates and hence it is obvious to prepare the ethanolate and solvates “*. The opponent has taken **obvious to try** approach which the applicant asserted to be improper in the present case. The **‘Obvious to try’** approach was applied long ago in case of ‘John- Mansville Case’ but this approach was criticized in ‘Conor-Medsystem Case’ and Saint Gobain case.. The obvious to try approach is applied only where there is a finite number of possibilities, it is known to a person skilled in the art and one of these possibilities would certainly work and hence the court may conclude that the claimed invention is obvious. In the present case there is a huge gap between prior art and the invention and there is a high level of improbability. On account of the above factors, the claimed invention is not obvious. The compound ‘X’ was only discussed in D1, it was not known whether the compound is amorphous or crystalline. It was not known which type of modification of the compound of formula ‘X’ would result in vastly enhanced pharmaceutical application and it was not known whether the amorphous/crystalline form could be modified and be put in pharmaceutical use and if so what modification and how it has to be effected. There may be general teaching

in the prior art exhibit C as to how solvates are generally prepared, it is simply not possible to anyone to predict from the structure of the compound whether a stable crystalline form can effectively be obtained or whether it is polymorphous or not and if so which of these form has the desired pharmaceutical properties. These things are only possible after experimentation only.

The applicant submitted that the opponent based on his exhibit C argued that *"the solvent used in the present invention are known and the solution of solvent will depend on the compound(s) sought to be stabilized"* –to this applicant replied that it is not obvious which solvent to choose, every compound is a different case ,sometime solvent for related compound will work sometime they will not. Applicant also refuted the argument of opponent that 1:1 is the common ratio and argued that there is no way of predicting what the stoichiometric ratio will be if a solvate is formed. It is not necessary that every molecule can work at 1:1 ratio. In the light of the above, the applicant argued that if 'windsurfing test'(windsurfing International Vs Tabur Marine ) is applied the claimed ethanolate solvate is not obvious. The applicant in support of their argument refer to a case law "**Arrow Generics case**" in which the applicant claimed a highly pure form of a crystalline Tibolone, the relevant prior art was 'Declereq' reference, which disclosed the process for the preparation of crystal of Tibolone The product Tibolone already in the market as 'Livial' . It was argued that preparation of highly pure crystalline form was obvious since a person in the pharmaceutical field being aware of therapeutic advantage of Tibolone would always try to prepare pure form and would come up with a highly pure crystalline form . The court held that there was a difference between the prior art and the claimed invention . The Declereq reference even if it identified a single crystal, never disclosed Tibolone of high purity and there was nothing in the prior art which would motivate a person skilled in the art to prepare highly pure crystal of Tibolone. Accordingly it was held the pure form of Tibolone is not obvious. The above case squarely applies to the present case where the prior art teaches the compound 'X' only. A person skilled in the art has to then find that whether the compound has pharmaceutical application or not ,explore various route to make

suitable pharmaceutical use. Therefore ethanolate solvent as claimed is not obvious.

Under section 3(d) , the applicant argued that the claimed pseudo polymorphs are excluded by virtue of section 3(d) as the applicant has proved that the prior art does not teach or disclose the improved stability of the claimed invention. The applicant admitted that the Court has in Novartis Vs Union of India, defined the efficacy which means the ability of the drug to produce the desired therapeutic effect and the Court has defined that the therapeutic effect means healing of disease / having a good effect on the body. The patent should disclose how effective the claimed invention would be in the healing of the disease or having a good effect on the body. But the applicant made a humble submission that the judgment of the Madras high Court is not binding and the meaning of the word enhanced efficacy is not limited to that given in the Novartis case and honorable controller is entitled to construe section 3(d) in accordance with the principle of interpretation of statute and that the claim should be given a positive construction.. The applicant insisted that the enhanced efficacy has to be construed in accordance with the facts of circumstances of the case. The ethanolate form of formula 'X' (Darunvir) when used with a low dose of Ritonavir shows greater efficacy against other protease inhibitors. It demonstrate its activity in vitro against wild type HIV-1 strain and multi drug resistance HIV strain and exhibited an extremely high bonding interaction with wild type HIV-1 protease.

To the opponent's argument that " ..the process of the preparation of the pseudo polymorphs obtained in the process claim are conventionally known step and must be rejected "the applicant replied that the applicant has demonstrated the inventive step of the claimed pseudo polymorphs over amorphous compound 'X' disclosed in 'D1' and therefore asserts that the opponent's allegation against the process claim is also traversed.

The applicant also referred to Han's statement, that it took a substantial amount of time, experiments and investigation to determine which solvates represent the best balance between the perspective of the methods for obtaining

the solvates i.e. the crystallization process on the one hand and pharmaceutical perspective of acceptability. It was found on these investigations that the best manufacturing isolation/crystallization and drying conditions to produce the ethanolate of compound 'X' in a 1:1 ratio. The test were conducted to establish better bioavailability of the ethanolate compound to the amorphous form. The ethanolate form shows substantially higher bioavailability and plasma concentration on its own or in combination with Ritonavir as compared to amorphous form. This is certainly to be considered an increase in efficiency and improved technical effect. Moreover the ethanolate and hydrate pseudo morphs have improved stability and chemical and crystallographic stability over this amorphous compound.

The opponent also referred to the Joel's Statement vide Para 32 & 36 of the said statement. The expert expressed that to address enhanced efficacy it is important to distinguish between potency & efficacy. He referred to Merck Manual for Medical information to say that “ ***Drug effect can be evaluated in terms of strength (Potency) or effectiveness (efficacy). Potency refers to the amount of drug (in mg) needed to produce an effect.*** Efficacy refers to the potential maximum therapeutic that a drug can produce. However greater potency or efficacy does not necessarily mean that one drug is preferable to another. When judging the relative merits of a drug for a patient, doctor consider many factor such as side effect, potential toxicity, duration of effect and cost.

The test of efficacy has been interpreted in Novartis Vs Union of India. The Madras High court defined the efficacy in terms in the field of pharmacology as “ ***the ability of the drug to produce the desired therapeutic effect and therapeutics defined as “ healing of disease or having a good effect on the body***”. The claimed invention has good effect on the body – that of healing HIV related infection. The healing effect is enhanced over the genetic potential of the molecular entity by providing a crystal form of formulation which in the eye of inventor, has the best combination of stability, solubility and bioavailability of the many prepared and characterized crystal forms.

The applicant submitted that the ethanolate solvate as claimed exhibit enhanced efficacy as compared to the amorphous form. The Novartis case accepts that the enhanced efficacy is to show therapeutic effect i.e. healing effect on the disease or having good effect on the body. However enhanced efficacy is not limited to a curative effect as clearly shown by the words having good effect on the body. Any improvement in stability and bioavailability enhances the therapeutic efficacy which has been described in the specification vide page 20, line 15-35. Stability examples vide example 6, page 26, Table 12 and example 8, 9 & 12. The applicant further pleaded that when a drug is given in powder or tablet form, the bio availability reduces because the body cannot absorb it completely or because of its fast metabolism. Bioavailability is physical property & fundamental for pharmacokinetics therefore knowing how to improve bioavailability can make a lot of difference. The applicant also pleaded that no comparison with novartis case could be made as argued by the opponent because that case is challenged and the order is reserved, the controller order has no binding effect in law and can not be ruled upon. Also in Novarties case bioavailability is direct consequence of higher solubility of the crystal form and for this reason the controller rejected the application whereas in the present case the ethanolate solvate exhibit 500% higher bioavailability as compared to the amorphous form and the same is not a consequence of greater solubility.

In respect of ground of insufficiency of description the applicant argued that the specification of the alleged invention provides different technical parameter of the polymorph form A in the XRPD data, DSC and TGA data etc . The XRPD solvate form A is at fig. -1 The distinction between Form A, Form B and the amorphous form is brought out clearly in fig 11-18. Form B has been characterized by IR,DSC,TGA and ADS/DES data vide page 31-32,table -18, the solubility and stability data in the Para 9.3 of the reply statement and in Para 18-22of Joel's statement .

To the objection of the opponent that "*the ethanolate solvate is claimed with crystal to solvent ratio of 5:1 to 1:5 but only solvate of ratio 1:1 has been substantiated in the specification* " , the applicant argued that the general

guidance was provided on Para 4 of page 7 ,the specific embodiment of the ethanolate solvate 1:1 is in the example 1 where it is explained. In this regard the applicant further argued that a single illustration was sufficient guidance to a skilled person and refers to a case law T 292/85 (page 3.1.5)

***“thus it is the view of the Board that an invention is sufficiently disclosed if at least one way is clearly indicated enabling the skilled person to carry out the invention , consequently, any non-availability of same particular variants of a functionally defined component feature of the invention is immaterial to sufficiency as long as there are suitable variant are known to the skilled person through the disclosure or common general knowledge which provide the same effect for the invention.....”*** Therefore there is no need to give an example and illustrate each and every part of ratio claimed. Also the opponent has not provided any evidence to demonstrate that ratio apart from 1:1 do not work. Therefore in the face of concrete example in the specification and in absence of evidence to the contrary, it must be taken that the invention has sufficiently been described. The applicant concluded the arguments

After hearing both the parties to the representation on the grounds of obviousness /lack of inventive step, not an invention / not patentable and insufficiency of description, I shall analyze the arguments of the parties evidence etc and give my considered view on each ground

The present application, after the submission of amendments of claims by the applicant, claims for two specific pseudo polymorphs, namely ethanolate and hydrate forms and their respective process of preparation etc.The application relates to pseudo polymorphs of compound ‘X’ namely ‘DURANAVIR’. This compound is disclosed in prior art document WO99/67417 as D1 in which compound ‘X’ was designated as compound 35 which is an analog of compound 32 of D1 which is useful in the treatment of HIV .The example 11 of the D1 clearly indicates that the compound 32 and its analog

(compound 'X') are predicted to be potent in preventing the selection of these viral strain in vivo. In the present invention it is mentioned that the compound 'X' has HIV protease inhibitory activity and particularly well suited for inhibiting HIV-1 and HIV-2 viruses.

The opponent has argued that the pseudo polymorphs of the present invention (ethanolates and solvates) are **obvious and lack in inventive step** in the light of prior art document D1 and exhibit A, B and C. I agree with the opponent statement that if the prior art knowledge and other cited documents provide motivation with reasonable expectation of success (but not a guarantee), that makes it obvious to try by a person skilled in the art. The exhibit A refers to a general method of preparation of shaped particle of crystalline organic compounds , a storage stable shaped particle of allotropic organic compounds, Exhibit A teaches that crystallization is a process by which polymorphs are formed with improved stability and bio availability. It also provides a list of commonly used solvents or solvent mixture to effect crystallization. It also teaches that the combination of size and shape of the particle and the uniformity and stability of the crystalline structure of the base organic compound lend particular predictability and consistent bioavailability etc.

In prior art document exhibit B (US 6096779 ) wherein for improving the slight solubility, it has been suggested to convert Piretanide form A in an acidic environment in the presence of lower aliphatic alcohol or a cyclic ether to a crystalline solvate form known as Piretanide B which showed improvement in the solubility in an acidic medium by 1.5 to 1.7 times as compared to base compound Piretanide A form and since pH of the gastric juices about 1, piretanide form B crystalline were suitable for oral administration . Although the prior art claims a polymorph of Piretanide by precipitation but the reference of the passage in the document clearly indicated that by crystallizing Piretanide form A in a lower alcohol or cyclic ether improves the solubility of the resulting piretanide polymorph form B in the acidic environment .

Exhibit C is a document titled "polymorphism in pharmaceutical solids" edited by Hang .G. .brittain. In the preface it says " ..... ***It was also established that the structure adopted by a given compound upon crystallization would exert a profound effect on the solid state properties e.g., volume density, surface tension diffusibility, refractive index ,melting point, heat of solution, solubility ,stability, hygroscopycity etc***". The same document while discussing solvent etc for preparing solvates mentions" ***...the most commonly encountered solvates among pharmaceuticals are those of 1:1 stoichiometry but occasionally mixed solvate species are encountered .For structure containing more than one solvent type , one generally finds non-polar solvents crystallizing together on the one hand and polar solvents on the other. For example ,the most common solvent found co-crystallizing with water are..., water, methylene dichloride, benzene, methanol, acetone ,chloroform and ethanol, THF etc.*** "The document provides preparation of many solvates of steroids, antibiotics and other pharmaceutical substances.

Therefore I find that the three exhibits clearly provide for general method of preparation, solvents and process parameters etc of shaped crystalline organic pharmaceutical substances and the properties that are associated with such crystallization particularly the improved stability, solubility and bio availability along with examples of Piretinide polymorph and other pharmaceutically useful substances like steroids, antibiotics etc. Various methods are available in these prior art for the preparation of solvates including hydrates using polar , non-polar and mixture of polar non-polar solvents. In the light of these exhibits, a person skilled in the art looking for stabilized form of compound 'X' of the present invention to achieve high stability and bioavailability would follow those established processes available in the prior art for preparation of polymorphs with reasonable expectation of success .As the preparation techniques are available in the prior art in detail along with commonly used

solvents and mixture thereof, a skilled person would select from the list of organic solvents, water and/or mixture thereof, depending upon the compound whose stability and bioavailability is sought to be improved and thereafter choosing from among the various polymorphs so prepared by routine trial and error method and verification of the property parameters arrive at the best form of polymorphs of pharmaceutical use.

The specification itself provide that all the process technique for pseudo polymorphs preparation are known in the art. The specification vide page 16 provide...”..... *pseudo polymorphs of the compound of formula ‘X’ are prepared by combining compound of formula ‘X’ with an organic solvent and water or mixture of water and water miscible organic solvents, applying a suitable techniques to induce crystallization and isolating the desired pseudo polymorph.....By technique for inducing crystallization are to be understood those processes for the production of crystals, which include dissolving or dispersing compound ‘X’ in solvent medium, bringing the solution or dispersion of desired concentration.....the technique for obtaining desired concentration are common in the art e.g., evaporation atmospheric distillation, vacuum distillation, fractional distillation etc,.....removing and/or separating any undesirable material or impurities may be performed by filtration, washing, precipitation or similar technique known to those skilled in the art can as well be used in the present process.... Drying procedure include all technique known to those skilled in the art, such as heating, applying vacuum, circulating air gas etc,....process of crystallization of pseudo polymorphs of compound ‘X’ embrace multiple combination of techniques and variation thereof,....”*

From the above passage of the specification, it clearly shows that the applicant has admitted the fact that the technique of the preparation of pseudo polymorphs are known in the art and a skilled person on the basis of common knowledge and the nature of the polymorph sought to be prepared, choose various techniques to optimize the product to pharmaceutical use.

The affidavit of Joel Bernstein mentions **that “....an amorphous active pharmaceutical ingredient (API) is generally an undesirable form because it is thermodynamically metastable with crystalline counterpart and does have the often desirable property of high solubility,.....it is often difficult to prepare, purify and to handle and if it is used as an API then there is always the possibility that it will be converted into a more stable crystalline form.....Hence in a drug development process the appearance of an amorphous solids usually generates considerable efforts to prepare crystalline form,.....but there is no guarantee of success at such efforts and even if successful the nature of the crystalline material and its characteristics can not be predicted prior to actually obtaining the product...when a crystalline form is prepared from an amorphous solid one generally expects improved stability but lower solubility.....”**

Further Han’s affidavit states **that pseudo polymorphs of compound ‘X’ has improved and enhanced stability and bio availability and that the applicant has unexpectedly found that it can be manipulated at higher purity for use as medicament against HIV protease.** Han’s statement of improved and enhanced stability ,solubility and bio availability could not be corroborated from the specification as no comparison of stability ,solubility and bio availability of form A and form B has been made against the base amorphous compound ‘X’ .Also contrary to the applicant’s repeated claim, the table 7-9.12-17,table 19-21and 24-26 and example 24, no comparative data with respect to the base amorphous compound ‘X’ has been given for stability ,solubility and bio availability in the present specification. These table shows the stability solubility of polymorph form A , form B and form K and the example 24 referred by the applicant is the comparison of the solvates with ‘PLACEBO’ as the control and not the compound ‘X’ for showing safety, tolerability and pharmacokinetics . Even the efficacy data provided by as annexure to the expert evidence does not have any data relating to the efficacy of the hydrate form over the compound ‘X’ .

From the above analysis following points clearly emerges;

- (1) That the techniques of polymorph preparation are known in the art. Exhibit A,B and C and many other prior art and publications are available which provide for various techniques ,such as selection of solvent, concentration ,separation , drying and crystallization etc. for preparing a polymorph of desired properties .
- (2) It is a established fact that the structure adopted by a given compound upon crystallization, would exert a profound effect on solid state properties e.g. crystal hardness crystal shape, solubility ,stability, dissolution ,bio availability density , viscosity , hygroscopicity , surface tension , rate of reaction etc.
- (3) Specification itself mention, that the different techniques of preparing polymorphs are available in the prior art and the common general knowledge .
- (4) From the prior art teaching of each document '693 and '779 , a person skilled in the art would easily note that crystalline polymorphs such as hydrates and solvates have better stability, improved solubility and bio availability compared to the basic amorphous form ,
- (5) The affidavit of Joel Bernstein vide page 28 admits that “an amorphous active pharmaceutical ingredient is generally undesirable because it is thermodynamically meta stable with crystalline counterpart and does have the often desirable property of high solubility,.....it is often difficult to prepare, purify and to handle and if it is used as an API then there is always the possibility that it will be converted into a more stable crystalline form.....Hence in a drug development process the appearance of an amorphous solids usually generates considerable efforts to prepare a crystalline form “ . Thus indicating clear motivation

for preparing polymorphs with a reasonable expectation of success to achieve a desired pseudo polymorphs of good pharmaceutical use.

- (6) The expert opinion in the affidavit of Joel Bernstein has admitted that the formation of pseudo polymorphs of the present invention was obvious to try although success was not guaranteed.
  
- (7) In Han's affidavit it states that ...." polymorphism of the compound 'X' has improved and enhanced stability, solubility and bio availability and that the applicant has unexpectedly found it can manufacture at high purity for medicament against HIV protease activity "The specification itself and the subsequent data submitted on affidavit, does not provide any data on purity or particularly any data regarding any enhanced efficacy of inhibiting HIV protease activity of the polymorph of compound 'X' compared to the base compound 'X'. The compound 'X' admittedly known for its role as HIV protease inhibition activity and it is obvious to presume that the pseudo polymorph of the same compound 'X' would have the same role as HIV protease inhibitor. In absence of any data for surprising effect/increase in efficacy in the inhibition of HIV protease activity preparation of polymorph of compound 'X' can not be regarded as having any inventive merit

I agree fully with the expert opinion (vide Para 5) that whenever the substance prepared is an amorphous active substance, it automatically generates considerable efforts to prepare a crystalline polymorphs which are generally found to be associated with higher stability and controlled solubility to help in achieving in the required bio availability of the active ingredients into the zone of reaction compared to the amorphous substance. Therefore whenever there is an amorphous active substance of interest, the product development process initiate efforts to convert the product into a more stable crystalline form with higher stability and lower / improved solubility. Hence there is always a

reasonable expectation of success in the conversion of stable crystalline form by method known per se but there is no guarantee of success that the efforts would result into a desirable product. If a person skilled in the art can on the basis of prior art and knowledge start putting efforts to convert API into a stable pseudo polymorphs with techniques known in the art and with a reasonable expectation of success to develop a stable product of desirable bio availability , such efforts will definitely amount to an obvious efforts. In other words when knowledge is available, techniques are available and there is a reasonable expectation in such efforts and only routine experimentation to find out which of the polymorphs are most suited for bringing the desirable effect ,by all means would be an obvious efforts. Also if a routine experimentation and verification of the data to choose which specific polymorphs would be most appropriate and for such experimentation, if time and money is spent, such efforts does not at all contribute to an inventive step under any circumstances.

From the above summarized points in the preceding Para, it is clear that the amorphous pharmaceutical active ingredient are undesirable due to its high solubility and dissolution rate. Also such substances are difficult to purify or handle during manufacturing process . Therefore it will motivate a skilled person in the art , in such case , to prepare pseudo polymorphs to improve processability and bio availability There are prior arts and other publication and text , available which provide for various process techniques including solvents etc. to prepare different form of polymorphs and Verifying from the data of different polymorphs by routine experimentation to select the forms best suited in the pharmaceutical activity. It is stated by Joel Bernstein that...."while it may be obvious to try, it is by no means obvious that such efforts will be successful "- Here it needs to be mentioned that when a skilled person in the art is motivated from the circumstances of the case to prepare with known process techniques with reasonable expectation of success ,it is immaterial whether he succeeds in his effort or not, such efforts would be definitely be obvious and bereft of any inventive merit. There is a clear motivation that solvates / hydrates of an

amorphous compound have higher stability and bio availability and a skilled person wishing to improve these properties of the drug, suitable for manufacturing and oral administration, would obviously try to form its solvates etc with reasonable expectation of success.

My views are strengthened with the Case Law - Merck 874 F.2d at 209 quoting in re Dow Chemical Co 837 F.2d 469,473 (Fed. Cir. 1988)

**“ 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 “**

Therefore I conclude that the pseudo polymorphs (solvates/hydrates) are known in the art including its preparation techniques and its properties. The applicant has merely carried out the routine experimentation to verify as to which among them are suitable as pharmaceutical active compound, with a reasonable expectation of success and achieve the result which was desired or expected and hence such polymorphs, its preparation process are obvious and does not involve any inventive step. Therefore the subject matter of claims represent an obvious solution to the problem underlying the present application and does not involve an inventive step.

In respect of the ground of **Not an invention /Not patentable**, as I have explained and concluded in the preceding Para that the present invention is obvious and lack in inventive step, therefore I conclude that the present invention is not an invention u/s 2 (1) (j) of the Patent Act 1970.

On the ground of **Not patentable u/s 3(d)**, the opponent argued that, the applicant has completely failed to demonstrate any therapeutic efficacy of the pseudo polymorphs of the compound of formula 'X' over the basic compound of formula 'X'. The applicant claimed that the invention has enhanced efficacy over known substances i.e. the pseudo polymorphic forms contribute to

the drug formulation of improved stability and enhanced bio availability and therefore qualifies the requirement of section 3(d).

As per the section 3(d) of the Patent Act 1970 , “.....mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of the substance....is not patentable.....” Further explanation in the section provides that the polymorphs or other derivatives of a known substance shall be considered to be the same substance unless they differ significantly in properties with regard to efficacy.

Therefore the crux of the section 3(d) remains that , a new form or a new derivatives of a known substance , as in the present case , shall not be patentable if it does not show any significant enhancement of the known efficacy compared to the basic compound .

In ***Novartis Vs Union of India & Others (2007) 4 MLJ 1153*** , wherein High Court has held ;

**“.....if the discovery of the new form of a known substance must be treated as invention, then the patent application should show that the substance so discovered has a better therapeutic effect ..”**

**“..... going by the meaning of efficacy and therapeutic extracted as above, what the patent application should show that the substance so discovered has a better therapeutic effect.”**

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

plasma concentration .Although I am not very convinced about the reliability of such data showing the bioavailability of the ethanolate polymorph vide TK3, page 3/6 and 5/6 of the annexure to the Han's evidence, wherein comparison were made with compound in capsule form. However I have accepted that comparison after subsequent explanation, given by the applicant, but the purpose of such comparison is hardly met. Again I found in the pharmaco-kinetic parameters, the comparison of AUC values varies by a large amount for one animal to other which makes the comparison data less reliable .In Han's affidavit it teaches that the ethanolate form the compound of formula 'X' when used with low dose of 'ritonavir' shows greater efficacy than other protein inhibitors , which is a statement and no data is placed .Moreover the statement discloses the combined effect of ethanolate and ritonavir , it is not clear whether the protease activity is due to ritonavir or ethanolate form . The present invention is not a combination of drug therefore , the therapeutic efficacy of the ethanolate polymorph ought to have been demonstrated alone .

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.

In respect of ground **of insufficiency of description**, I agree that after the filing of amended claims by the applicant wherein claims are directed to ethanolate polymorphs and hydrate polymorphs only , the insufficiency ground is partially met. However the invention is still not enabled with respect to the claim of ethanolate polymorphs with wide range of compound to solvent ratio of 5:1 to 1:5. Only 1:1 ratio ethanolate form A was enabled by way of example. -1 but no enablement for other ethanolate polymorph forms with varied compound to solvent ratio . Claim -7 of the amended claims provide for a process for preparing an eyhanolate polymorph comprising the step of combining (3R,2as,6ar )-hexahydrofluoro [2,3-b]furan 3-yl (1S2R)-3- [(4-aminophenyl)sulfonyl (isobutyl ) amino-1-benzyl-2-hydroxypropyl carbamet ,with ethanol or mixture of water and ethanol and inducing crystallization. The claim does not identify the product whether it is a single solvate or a mixture of solvates. Claim -7 appears to be multiple solvates comprising many other solvates such as monosolvate , di solvate or mono ethanol- mono hydrate etc. each solvate is an independent chemical material having distinct chemical identity with different physical and chemical properties. No detail explanation is provided in the specification to define the scope and the enablement of the invention. Example -1 enables to prepare form A (1:1) i.e. a specific pseudo polymorph A (1:1) having its distinct physico chemical properties. But this example in my opinion can not sufficiently provide enablement for other solvates between 5:1 to 1:5 because following the same procedure it is difficult to believe that all the pseudo polymorphs possible between the said range of 5:1 to 1:5, can be separately recovered, by following the same recovery process and can be identified and characterized.

Claim-11- a hydrate form B, for which no enabling process has been distinctly defined. The efficacy values given during prosecution as annexure to expert evidence of Han's, does not provide any data relating to the efficacy of hydrate form B. Therefore I agree with the arguments of the opponent that the applicant has failed to provide sufficient description in the body of specification .Also it is to be noted that the therapeutic comparative data of the ethanolate and the solvate form with respect to the base compound of formula 'X' has neither been provided in the specification nor any such comparative data , provided in the form of an affidavit during the prosecution .Except a reference made by the expert Hans that *the ethanolate form the compound of formula 'X' when used with low dose of 'ritonavir' shows greater efficacy than other protein inhibitors* , which is a mere tatement and no data is placed in favour of the said statement and particularly with respect to ethanolate or solvate forms alone. Therefore on the basis of above finding I conclude that the application fails to provide sufficient description required under section 10 of the Act.

Here it is pertinent to note that the claim of composition with diluent or carrier of the polymorph can not be claimed as the polymorph will lose its identity on mixing with liquid and convert into the base compound of formula 'X'. Claim 18 is a Swedish type claim is not allowed as per the common general practice being not an invention.

In view of my findings in the preceding paragraphs, I conclude that the present invention as claimed in revised claim 1 to 18 of the application number 3598/DELNP/2004 is;

- (a) Obvious and does not involve an inventive step over the prior art mention therein
- (b) Not an invention within the meaning of section 2(1)(j) of the Patent Act 1970;

- (c) Is not patentable invention within the meaning of section 3(d) of the Patents (Amendment) Act ;
- (d) Is lacking in sufficiency of description of the invention

On the basis of the above findings and the circumstances of the case I refuse to proceed with the application number 3598/DELNP/2004 for grant of patent.

The application stands disposed with no cost to either party.

Dated this, the day of 6<sup>th</sup> July, 2009

(S.K. Roy)

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