THE PATENTS ACT, 1970

SECTION 25(1)

In the matter of the Application
For Patent No.841/DEL/1996
Filed on 19th April, 1998
and
In the matter of a representation
Under section 25(1) of the Patents
Act, 1970 as amended by the
Patents (Amendment) Act, 2005
and
In the matter of rule 55 of the
Patent Rules, 2003 as amended
by the Patents (Amendment)
Rules, 2005.

M/s Astrazeneca UK Limited, UK ……. The Applicant

M/s G M Pharma Ltd., India …….. The Opponent

Hearing held on 21st march,2007

Present:

M/s Ranjana Mehta — Agents for the Applicant

M/s Deepa Kittoo

Mr. S. Majumdar — Agent for the opponent

DECISION

A representation by way of opposition under section 25(1) of the Patents Act as amended by Patents (Amendment) Act, 2005 was filed by M/s GM Pharma Ltd. on 21st November, 2006 with a request for hearing u/r 55 of the Patents Rules, 2003 as amended by Patents (Amendment) Rules, 2005. Accordingly the applicant also submitted the reply statement and evidence on 26th February, 2007 with a request for hearing u/r 55 of the Patents (Amendment)

Act, 2005.Hearing was fixed to be held on 21st March ,2007 and both the party to the opposition attended the hearing on the scheduled date.

Before I proceed with various grounds of opposition, a brief background of the application is necessary. An application for patent claiming U.K. priority with priority date 27th April 1995 for an invention titled "Quinazoline derivative (claim 1 to 10) process thereof and pharmaceutical composition, was filed on 19th April, 1996 , by the agent to the applicant. The opposition in the written statement raised following grounds of opposition.

(1) Wrongfully obtaining 25(1)(a)
(2) Lack of novelty (25(1)(b) & C
(3) (3) Prior use/Publicly known 25(1)(d)
(4) Lack of inventiveness 25(1)(e)
(5) Information under section 8 , u/s25(1)(b)
(6) Not an invention/not patentable under section 25(1)(b)
(7) Insufficiency 25(1)(g)

and submitted following supporting documents along with the statement ;

(1) EP/0566226 A1(exhibit 1), (2)Administrative documents submitted to CDER and new drug approval for gefitinib (Exhibit 2)

Applicant in the reply statement submitted two supporting documents including one evidence (1)Comparative test data by Mr . J.R.Woodburn (2)Additional test data by Mr. J R Woodburn .

Before the date of hearing, the opponent were issued the amended claims submitted to this office by the applicant during the examination and communications of objection. Therefore the opponent argued on the basis of amended claims during hearing.

During the hearing opponent only argued in respect of the grounds of (a) Anticipation, (b) Lack of inventive step, (c) Prior Public Knowledge & (d) Not an invention/not patentable.

Now I shall consider the arguments given by Shri S. Majumdar, agent for the opponent in respect of ground of anticipation.

In respect of the ground of anticipation by prior publication ,opponent relied in their submission upon the document EP/0566226, titled "Quinazoline Derivative" ,was filed on January 15 1993 claiming priority date of January 20,1992,June 26,1992 and November 12,1992 of GB. It was published on October 20,1993. During hearing the opponent argued with reference to US/5457105 (hereinafter D1), which is equivalent to and has the same contents as EP/0566226.Opponent crave leave to refer to disclosure of US/5457105 for convenience of the identification of the relevant pages. The opponent compared the substitutents at R1□ & R², position of the claim 1 of the application with disclosure US/5457105 (D □) wherein in the R² position 3' fluoro 4'-chloro and 3, 4 difluoro, claimed in the present invention had been generically disclosed vide column 10, line 48-49 wherein R² is chloro, fluoro Bromo or Iodo. Again 3'-chloro –4' fluoro was specifically disclosed in column 15, line 15 under preferred aspect and 3' 4' dichloro was specifically disclosed under column 15, line 14-15 under preferred aspects of the invention of the said prior art D□. At R□ position , at the 6th position of the quinozoline, the substitutent , 2 dimethyl aminoethoxy, 2-diethyl aminoethoxy were specifically disclosed at column 8, line 36 & 37, 3-dimethyl aminopropoxy and 3-diethyl amonopropoxy were specifically disclosed under column 8, line 39 and 40. The substitutent 2-piperidino ethoxy & 3-piperidino propoxy werre specifically disclosed at column 8 line 56 and 57 and substituent 2-morpholino ethoxy, 3-morpholino propoxy & 2-(4 methyl peperozin-1yl) ethoxy were specifically disclosed at column 8 line 59, 60 & 63. At the same time opponent accepted the fact that the substituents 2-(Pyrrolidin-1-yl) ethoxy, 3-(Pyrrolidin-1-yl) propoxy, 2-(imidazol-1-yl)ehoxy, 3-(imidazol-1-yl) propoxy, 2-[di(2-methoxyethyl) amino] ethoxy and 3-morpholino-2 hydroxy propoxy were not specifically disclosed in the prior art.

The present invention claims Methoxy group at 7th position of the quinozoline molecule, which had been specifically disclosed at various pages within the said

prior art document at column 12 line 36, column 13 line 12, column 13 line 23, column 14 line 30 & 65.

Opponent also mentioned that the claim direct to the said formula 1 of the present application where in R2 is 3' fluoro, 4' chloro, is 3'4' difluoro and wherein R□ may be selected from 2 (pyrrolidin-1-yl) ethoxy, 2-(pyrrolidin-1-yl) propoxy, 2(Imidazole-1-yl) ethoxy,3-(imidazole-1-yl) propoxy, 2(di-(2-methoxy ethyl) amino] ethoxy and 3-morpholino-2-hydroxy propoxy are novel over prior art document D□. Therefore substantial portion of the amended claims of the opposed application except the above said novel compounds , is anticipated by the prior art.

Opponent further argued that subsequent claim 2 of the opposed application is novel as 2-(pyrrolidin)-1-yl) ethoxy substutuent was not disclosed in the prior art as the preferred substituent at 6th position. Claim 3 of the opposed application is not novel over prior art reference which clearly taught 3' chloro 4' fluoro substituent (column 15, line 15), 7-methoxy substitutent (column 12 line 63 etc.) and 2-morpholino ethoxy (column 8 line 59). Claim 4 of the present invention is not novel on the face of prior art reference which clearly taught 3' chloro, 4' fluoro substituent (column 15, line 15) the 7-methoxy substituent (column 12 line 63) and 3-diethyl amino propoxy at 6th position (column 8 line 40). Claim 5 and claim 7 of the present invention are novel over prior art as the substituent at 6th position in these claims were not disclosed in the prior art.

Claim 8 of the present application is not novel over the prior art because all the three substituent of this claim compound were suggested under preferred aspect of the prior art D, i.e 3-chloro 4-fluoro substituent (taught at column 15 line 15) the 7-methoxy substituent (column 12 line 63) and 3-piperidino propoxy (column 8 line 57).

Claim 9 of the present application is not novel on the face of the prior art reference under preferred aspect i.e. 3—chloro 4'fluoro substituent (column 15 line 15), 7-mehtoxy substituent (column 12 line 63) and 3-morpholino propoxy (column 8, line 60).

Accordingly the subsequent claims 3,4,6,8,9 are anticipated and claims 2,4, & 5 are novel over document D1. Claim 10 which is a hydrochloride salt of the derivative of the formula claimed in claim 9 is also not novel because suitable pharmaceutically acceptable salts of quinozoline derivatives of the invention including hydrochloride salt has been disclosed in column 10 of line 51 to 58 of the document D□.

The process claim 11 is also not novel on the face of column 15 of D□ and also the third paragraph of page 13 of the applicant specification which admits that the claimed compounds may be prepared by any process known , to be applicable to the preparation of chemically related compounds. It further says that suitable process includes those illustrated in EP Application No.0520722 & 566226 (the European equivalent of D□). Also the pharmaceutical composition is also not novel on the face of DI. The opponent argued that the said claim is directed to known quinozoline derivative (anticipated by DI) in association with conventional pharmaceutical feature that render the claimed subject matter not novel over document DI.

Opponent further argued that the applicant is merely attempting to claim prior art in the guise of selection patent and referred to a cited decision T-0124/87 of European technical board of appeal.

Which said that ***"If the prior art is a written document then what is to be considered is that whether the disclosure of the document as a whole is such as to make available to a skilled man in the art as a technical teaching the subject matter for which protection is sought in the claim of disputed patent" further if a prior art document describes a process for the production of a class of compounds, the member of the class being defined as being any combination of values of particular parameters within numerical ranges for each of those parameters, and if all the members of the defined class of compounds can be prepared by the skilled person following such teachings, all such members are thereby made available to the public and form part of the state of the art, and a claim which defines a class of compound which overlaps the described class lacks novelty. This***

holds even when the specifically described example in the prior art document only prepares compounds whose parameters are outside the claimed class" In the present case also a person skilled in the art could have readily prepared the claimed compound using the process disclosed in the prior art particularly when the essential feature of the presently claimed invention being the 7-methoxy position on the quinozoline molecular and R2 as 3'4 diholo substitutents, are clearly taught as most favoured embodiment disclosed in the prior art. Therefore claimed invention is clearly anticipated by the prior art.

The opponent relied upon *Ranbaxy UK Limited and Arrow Generics Limited Vs Warner Lambert Company, In the High Court of Justice ,Chancery Division ,Patent Court ,Judgment ordered by the Honourable Mr. Justice Pumpfrey.* This is the judgment in two action brought by Ranbaxy(UK) Limited and an action by Arrow Generics Limited respectively against Warner Lambert Company. Warner Lambert is the owner of the EP patent EP/(UK) 00247633 and the EP/(UK) 0409281 which are concerned with Atorvastatine , a cholesterol synthesis inhibitor of great commercial importance. The calcium salt is sold under the name 'lipitor'. So far as '281 was concerned the issue were obviousness over the application for the '633 patent and anticipation by Warner Lambert application no. WO89/07598

The Ld Judge in ruling on anticipation dealt with the issue of anticipation as;

"The circumstances emphasise the importance of not drifting away from the strict principle of anticipation, which are` set out in General Tire Vs Firestone [1972] RPC 457 at 485. For a claim to be anticipated by a prior disclosure, the prior disclosure must contain a clear description of ,or clear instruction to do, or make ,something that would infringe the patentee's claim if carried out after the grant of the patentee's patent . If ,on the other hand, the prior publication contains a direction which is capable of being carried out in a manner which would infringe the patentee's claim, but would be at least as likely to be carried out in a way which would not do so, the patentee's claim will not have been anticipated, although it may fail on the grounds of obviousness. A signpost however clear, upon the road of

the patentee's invention will not suffice. The prior inventor must be clearly shown to have planted his flag at the precise destination before the patentee".

The claimed invention in the above patent suit related to hemi-calcium salt of Atorvastatine whereas the prior art generically disclosed salt of atorvastatine as hereunder;

*'**In the ring opened dihydroxy acid form, compounds of the present invention react to form salts with pharmaceutically acceptable metal and amine cation formed from organic and inorganic bases, The term "pharmaceutically acceptable metal salt " contemplates salts formed with the sodium, calcium. magnesium, aluminum, iron and zinc ions '.***

I conclude that this is a clear case of anticipation of claim 1 of '281 . '581 gives specific direction to make the three preferred enantiomers, one of which falls within the claim.

The opponent stated that the facts of the case are applicable to the present case as well. It has been concluded in the above cited case that it does not matter whether the disclosure in the prior art is by formula or by enumeration. The prior art clearly taught the claimed compounds by reciting the precise substituents, which anticipates the claim of the opposed application, therefore the specific salt claim 10 is` specifically anticipated by the prior art.

The opponent further argued that in the same judgment the Ld Judge ruled extensively on the patentability of the selection inventions

(a) There is no doubt that where there is a disclosure of a class of compounds , it is possible to select from the class, a subclass united by a common feature distinguishing it from the rest. These are so called selection patents. A fortiori, it is possible to select a single compound having advantageous properties from a class----IG Farbenindudtrie AG's patent (1930) 47 RPC 289 - But underlying this principle is the necessity for the prior disclosure to be a disclosure of a class, rather than a disclosure of the individual members `of the class as distinct entities.

The prior art of record clearly identifies the various substituents i.e., the specific disclosure of all the claimed substituents on the 6th position together with the preferred and most preferred disclosure of 7-methoxy and 3,4 dihalo substituted 4-anilino,lead to clear anticipation of the present claims.

Opponent further argued that the law relating to selection patent has been authoritatively stated by the House of Lords in E.I. du. Pont. De Nemours & Company (wetsiepe's) Application (1982) F.S.R. 303 ***"…….where a substance is already known, a discovery that the disclosed or the known substance has some or useful quality not previously recognized, does not give a right to patent".*** Also they referred to another statement by Lord Diplock ***"The inventive step in a selection patent lies in the discovery that one or more member of a previously known class of products process some special advantage for a particular purpose, which could not be predicted before the discovery was "made"*** (In R3. I.G. Farben industrie A-G'S Patents (1930) 47R.P.C. 283 PER Maugham J. at pp 323/3)…..(Beecham Group Ltd. vs Bristol Laboratories International S.A. [1978] RPC 521 at 579).

Accordingly, the opponent argued, that a selection patent may thus be granted only when certain member of a previously known class posses properties that were completely unsuspected & unpredictable and the fact that some member of the class work better than other is no ground for the grant of selection patent. In the present case '226 patent discloses compounds that had anticancer properties and in the opposed application too have anti-cancer properties. There was nothing unexpected, surprising or unpredictable about the compound & therefore patent cannot be granted to the applications.

Opponent again referred to a case Law E.I. Du. Pont de. Nemours (Wetsiepe's) application (1982) FSR 303 wherein Lord Wilberforce explained that a selection patent will not be prior published if ***"(a) all the selected members of the class possess the advantage (b) the later specification discloses what that advantage is (c) the prior publication of the wider class does not refer to that advantage".*** The applicant has failed to demonstrate that all of the claimed compounds possess surprising properties. Because the comparison has

not been made with the closest prior art, the advantage has not been brought out in the specification and the prior art discloses the same utility of the claimed compound as that being claimed in the opposed application. The advantage have not been brought out in the specification or in the comparative test data provided by the applicant. The prior art clearly discloses the same utility of the claimed compound as that being claimed in the opposed application. ***(d)In order to leave open a field for selection by a subsequent inventor, it does not matter whether the original field is described by formula or by enumeration .A skilled chemist could , in most cases quite easily transform the one into the other and the right of the subsequent inventor can not depend on the notation used .***The disclosure of specific substituents at the 6th position together with a clear cut description of 7-methoxy and 3',4' dihalo substituted4-anilino group clearly anticipate the claimed compounds. ***(e)The size of the initial group or class is not in itself decisive as to the question of prior publication of an invention related to a selected member or members……The size of the class may be relevant to a question of obviousness, and that question in turn may depend in part ,upon whether the latter invention relates to the same field as that occupied by the prior invention, or to a different field……..Therefore unless the latter patent states what the advantage possessed by the selected class, it is merely an arbitrary selection ,among thing already disclosed ,and will lack novelty.*** Opponent stated that the alleged invention relied upon by the applicant do not substantiate the claim for a new invention

The opponent refuted the submission of the applicant that the drug 'IRESSA', the pharmaceutical active ingredients of which is provided in Example 1 of the present application, but the same was not disclosed in EP566226. In this regard they argued that the NDA application filed by the applicant i.e. ND 21-399, regarding 'IRESSA' (Gefitinib) which is the compound also being claimed in this opposed application. The paragraph A(7)(b) of the said NDA application states US patent number 54,57,105, contains drug substance claims, pharmaceutical composition claims and method of use claims, and in paragraph

A(7)(e) it further states". The undersigned declares that US patent No.54,57,105 covers the formulation composition and method of use of 'IRESSA' (Gefitinib tables). The product is a subject of this new drug application for which approval is being sought". Opponent argued that this declaration alone clearly demonstrates that the claimed invention is a mere attempt to reinvent the prior art and reclaim a knowledge which has already lapsed into the public domain, because the prior art US 54,57,105 cannot claim IRESSA until and unless it discloses that molecule.

The applicant strongly resisted the opponents allegation that those functional group at R' and R^2 position as mentioned by the opponent are disclosed in '226 document and stated that the present invention in a selection invention and the compounds claimed are not disclosed in the prior art document. Novelty in the present application resides in the particular positioning of the functional groups at position 4^{th}, in the aniline ring and 6^{th} & 7^{th} position in quinazoline ring. A selection invention may well be encompassed by claims granted from a parent patent application nevertheless the subject matter of the selection invention is still novel if its scope doesn't embraces any subject matter that was specifically disclosed with parent application.

The applicant also refuted the argument of the opponent that the present invention can not be a selection invention and submitted that mere disclosure of functional group specification doesn't in any way teaches a person skilled in the art which functional group to choose and where to locate them in order to achieve enhanced or surprised effect. Although functional groups have been disclosed in the prior art but the specific combination of the functional group and their specific substitution / locations have not been disclosed.

Applicant also submitted that out of 103 compounds disclosed in 80 examples only 18 of the 103 compounds encompassed 'halogenoanilino' substituted group whereas all the compounds encompassed in the present application are 'halogenoanlino' substituted compounds but there is no disclosure of any compound of the present application (with respect to all the three substituents)in any of the 103 compounds disclosed in 80 examples of the prior

art. Therefore said functional groups are not disclosed in the same specific combination and position and it cannot be held that the said compound anticipates the present compound. The applicant also denied the opponent's argument regarding the disclosure of IRESSA (gefetinib) which is disclosed in present application vide example 1, has been disclosed in the earlier patent. Applicant argued that the example 1 of the instant invention relates to IRESSA which is a selection from the earlier patent of the applicant. The present application directs to specific compounds with specifically chosen functional group at specifically chosen position and posses significantly enhanced therapeutic properties vis-à-vis compound disclosed in the prior art. Therefore we strongly assert that the IRESSA is no where specifically disclosed prior art.

Applicant referred to this tribunal, a judgment from fleet Street Report 1982 E.I. Du point De Nemours and Co. (witsiepe's) application. vide para 4 page 304.

"Disclosing a prior invention does not amount to prior publication of a later invention if the former merely points the way which might lead to the later. The alleged prior disclosure must clearly indicate that use of the relevant material (i.e. that ultimately selected) does result in a product having the advantages indicated for the class. It is the absence of the discovery of special advantages as well as the fact of non making, that makes if possible for subsequent researchers to make an invention related to a member of that class".

The applicant also referred to a judgment submitted by the opponent i.e. High Court of Justice Chancary Division Patent's Court, Ranbaxy U.K. Ltd. and Arrow Generies Ltd. vs Warner Lambert Co. ***"For a claim to be anticipated by a prior disclosure, the prior disclosure must contain a clear description of or clear instruction to do or make. Something that would infringe the patentee's claim if carried out after the grant of the patentee's patent. ……..A signpost however clear, upon the road to the patentee's invention will not suffice. The prior invention must be clearly shown to have planted his flag at the precise destination before the patentee".*** The above passage

is completely relevant to the present application, since the prior publication does not explicitly or implicitly , teaches those compounds claimed in the present application. Moreover, it has not even implicitly been disclosed since the person skilled in the art would have to conduct research and experimentation to arrive at the particular combination of the functional group encompassed by the present application and would not in any way have been inevitably arrived at the claimed compound that have remarkable superior efficacy as compared the prior art. Therefore we strongly resist the opponent's allegation of anticipation by the '226 patent & claim that the present application is a novel subject.

The applicant further stated that the structural novelty of the compound of the present invention resides in that, they have a limited number of particular substituent at each of 4^{th} ,6^{th} and 7^{th} position of the quinazoline ring .The applicant considers that the opponent is trying to mislead the Honorable Tribunal by deliberately confusing 'encompassed and disclosed' subject matter. The opponent statement is also misleading wherein it stated" EPA/0566226 particularly relates to quinazoline derivative represented by the formula (1) wherein 4-aminoquinazoline compound possessing a 7-alkoxy substituent and a 6-amino alkoxy substituent are disclosed .It is submitted that no such compound is disclosed their in. The applicant strongly asserted that the opponent is wrong in stating that the compounds now being claimed are not novel and have been disclosed in EP/0566226. Applicant invited the attention of the Tribunal to the description of the Exhibit EP/0566226 i.e.; the prior art which discloses the broad generic compound from which the specific substituted compound of the present invention is derived. The applicant also countered that the drug IRESSA (gefitinib) the pharmacologically active ingredients of which provides example 1 within the present application is claimed within the 10 claim of the prior art EP/0566226 and submitted that internationally accepted standard for a selection patent is that the compounds claimed in the selection invention must be novel i.e.; must not have been disclosed specifically within any earlier patent application and must possess surprising properties compared to the properties

of the closest compounds that were specifically disclosed with in the earlier patent application.

The applicant also submitted that the corresponding patent application has been granted in many countries around the` world .All these patent offices , granted the patent have accepted that the subject matter of the present invention is novel and possess surprising properties compared to the closest compound that was specifically disclosed in the earlier publication. The drug IRESSA ,the pharmacologically active ingredient of which provided in example 1 within the present application lies within the area of overlap of the present application and exhibit 1, ie;EP/0566226. However IRESSA (gefitinib) is not disclosed as a patent example within the earlier patent EP/0566226

The applicant argued that there is an overlap of the scope of the original claim 1 of the present application and the scope of EP/0566226 when R1 in each application is (located at 6^{th} position of the quinazoline ring) a di-[(1-4C) alkylamino-(2-4C)alkoxy or morpholino-(2-4C)alkoxy or piperazin-1-yl-(2-4C)alkoxy group. That does not mean that the present invention lacks novelty as there are no compounds disclosed in EP/0566226 that specifically lie within the area of overlap.

The applicant submitted that comparative test data were presented before the international patent examiner by way of statement,dated,21^{st},1997 by Mr. J R Woodburn for the compound of the present invention and for compound from the patent EP/0566226, corresponding international patent applicationPCT/GB96/00961 filed on 23^{rd} April 1996and gave rise to WO 96/33980. The statement provides the test data concerning the activity of example 26,41and 64 from EP/0566226 and the example of PCT/GB96/00961 establish;

(a) That , in general ,both groups of compounds possess similar potencies in vitro as inhibitor of the enzyme EGF receptor tyrosine kinase

(b) that in general ,example 26,41and 64 of EP/0566226 are surprisingly less potent than the example of PCT/GB96/00961 in vitro as inhibitor of the EGF-stimulated growth of KB cancer cells.

(c) In particular that at the test doses of 50 and/or 200 mg/kg/day, example 26,41 and64 do not demonstrate statistically significant inhibitory activity in vivo against the growth in nude mice of human-431 tumor fragment and do not attain more than50%tumor inhibition.

Whereas in general example of PCT/GB96/00961 do unexpectedly demonstrate significant inhibitory activity in vivo in the anti-tumor test at test doses of50 mg/kg/day with 13 of the 20 example and especially example 1 and 3 of the PCT/GB96/00961 do unexpectedly demonstrate more than 50% tumor inhibition at a test dose of 12.5 mg/kg/day.

Therefore the comparative test data together with the proper analysis of the extent of disclosure in EP/0566226 demonstrate that the standard for the patentability of selection invention has been met. The compounds claimed in the selection invention is novel and they possess surprising properties compared to the properties of the closest compound that were specifically disclosed in the earlier patent application.

The applicant also countered the opponent argument of claim6 of EP/566226 where a list of R1 group is provided. Substituent at 6^{th} or7th position or as a pair located at these positions. There is a list of 37 possibilities, none of these mentions a group at the 6^{th} position that falls within the generic term dialkylaminoalkoxy. Similarly in claim 5 of EP/0566226 allows the R1 group to be located at the 6^{th} or 7^{th} position there is a list of 73 possibilities , just 5 of which falls within the generic term dialkylaminoalkoxy such as 2-dimethylaminoethoxy group or 2-morpholinoethoxy group. Therefore the applicant stated that ,there is no particular focus in the preferred aspect of the invention disclosed in EP/0566226. on the important element of a diakylaminoalkoxy group at 6^{th} position on the quinazoline ring. In particular there is no disclosure of quinazoline compounds which bears a dialkylaminoalkoxy at the 6^{th} position and which also have an alkoxy substituent at the 7^{th} position. Therefore the present invention is sufficiently removed from the preferred aspect of the earlier invention.

Inventive step /obviousness

The opponent argued that the alleged invention includes compounds wherein R2 substituent may be 3'-fluoro-4'-chloro and 3',4' di fluoro in addition to 3'-chloro-4'-fluoro and 3',4'-dichloro,which are already taught in the prior art. While the specification only discloses 3'-chloro-4'-fluoro and 3'-4'-dichloro in the text. Therefore prima-facie obviousness has been made by the opponent in view of the close proximity of the prior art and in absence of any data based showing of inventive step as to how the reversal of halogen atom in 3'-fluoro-4'-chloro or the substitution of chlorine in 3',4'-difluoro for the two fluorine atoms provide advantage over prior art. The opponent stated that7-methoxy substituent has been specifically disclosed in the prior art. The claimed compounds encompasses at the 6^{th} position 2-(pyrrolidin-1-yl)ethoxy which is the product by alkoxylation of pyrrrolidin-1-yl substituent of prior art D1 similarly 3-(pyrrolidin-1-yl)propoxyprepared by alkoxylation of pyrrolidin-1-yl substituent of the prior art ,2-(imidazol-1-yl)propoxy or 3-(imidazol-1-yl)propoxy whereas the prior art discloses (piperazin-1-yl)ethoxy substituent ,similarly 2-[di-(methoxyethyl)amino]ethoxy which is an alkoxylation product of alkoxy amino substituent disclosed in D1 and 3-morpholino-2-hydroxy propoxy which is a hydroxylation product of 3-morpholino subsituent of the prior art D1. In all these substituent of the present invention the applicant has failed to provide any data based evidence to show as to how the the said alkoxylation or hydroxylation of the prior-art substituent confers inventive merit on the claimed compound. Therefore subject matter of claims 1,2,5 and 7are clearly obvious and devoid of inventive step as the compound claimed there in are obvious derivatives of the compound disclosed inD1.

The opponent submitted that the present application claims Gefitinib in claim 14 and 15 as originally filed. This compound is taught in exhibit no.1. Compound 5e disclosed in Table III on page 37 and covered in claim 7 of exhibit –1 encompasses the two of the substituent present in the gefitinib compound i.e. compound 5e has R_2 as 3'-chloro-4'-fluoro and R_1 as methoxy which is present at both 6^{th} and 7^{th} position .,thus a morpholinopropoxy to be present at 6^{th}

position which is claimed and taught in exhibit –1 would easily motivate a person to replace the methoxy at 6th position of compound 5e with morpholinopropoxy to get gefitinib besides its hydrochloride salt is also taught in exhibit –1.

Opponent further submitted that the comp[ounds of the alleged onvention possess anti-proliferative properties which are believed to arise from Class 1 receptor tyrosine kinase inhibitory activity. The document D1 vide column –2 line 21-26 also discloses ….."***certain quinazoline derivatives possess anti cancer properties which are believed to arise from their receptor tyrosine kinase inhibitory properties…….Many quinazoline derivatives are already known but we are not aware of any public disclosure that any such quinazoline derivatie possess anti-cancer properties arising from receptor tyrosine kinase inhibitory properties"*** .Therefore claimed compound possess the same anti proliferative activity .Document D1 clearly states at several places that anti cancer properties are expected of the compounds disclosed therein. Therefore the alleged invention is a blatant attempt to claim the prior art and create monopoly over the compounds, which are in public domain.

The opponent also resisted the argument of the applicant 's statement set forth in support of novelty that the alleged invention does not embraces any of the compounds specifically disclosed as example in the prior art ,because the person skilled in the art is able to perceive all compounds covered by the chemical structure provided in the patent specification, whether or not all such compounds covered by the structure are specifically described or illustrated.

The opponent also denied that the comparative test data provided in the statement dated January 21,1997 by Mr. J R Woodburn substantiate the fact that the compounds claimed in the opposed application possess surprising properties compared to the properties of the closest compound that were specifically disclosed within the prior art .The efficacy data presented in the specification is for 23 compounds , whereas ,the claimed scope includes 60 compounds within its scope. And therefore failed miserably to demonstrate the presence of surprising effect over the entire claimed scope. Even if the data provided in the

said declaration no.1, the applicant has compared the IC_{50} values of the compared molecules, which is defined as the minimum inhibitory concentration of the compound required to inhibit 50% of a test target. This means the lower the IC_{50} Value of a tested compound ,higher would be its activity. Opponent therefore denies that IC_{50} values are the correct parameter to test the efficacy of a compound ,as it may be possible that a compound having higher activity may also be highly toxic. Opponent stated that the more reliable parameter for testing the efficacy of a compound is the therapeutic index. The lower the therapeutic index better is the efficacy of a drug for a desired activity. But the applicant has failed to provide the therapeutic data of the claimed compounds vis-à-vis the therapeutic values of the closest prior art. Even if IC_{50} data are representative of a compound's activity the data set forth by the applicant do not establish the inventive step. The most potent compound of the prior art selected by the applicant is the compound of example 41 of the prior art. Except the compounds of example 1,3,4,6and 9,all other compounds are less active than the prior art compound of example 41 as their IC_{50} values are greater than the IC_{50} values of the most potent compound of the prior art. The most active compounds of example 1,3,4,6and 9 are 1.45 to2.9 times more potent than the compound of example 41.when a large number of compounds are disclosed variation of the order of 2-3 times are only expected. And such variation in a selection of a class within the prior disclosed broad class of compounds only at best 2.9 times activity can not be called as unexpected activity for claiming inventive step.

In another test sample provided by the applicant it is evident that compound of example 2 is 1.06 times ,compound of example 3 is 1.85 times, compound of example 8 is 1.90 times ,compound of example 19 is 1.64 times and compound of example 20 is 1.35 times , active as compared to the compound of example 41 of the prior art which covers a substantial scope of the claimed invention only possess equivalent potency to most active compound .The most active compounds of the claimed invention are the compounds of the example 1, 4, 6 and 9 consistent with the finding under test condition (a) and are only 7.4times more active than the compound of example 41 of the prior art.. The opponent

stated that in view of the expected variation in the activities of the compounds when the prior art discloses a large class of compounds a section of a class of compound that the selected class displays only 7.4 times activity which can not be termed as unexpected.

Under Table 2 the applicant has furnished data regarding the dose-response relationship and compared the same with the dose-response date of the compound of the prior art. opponent argued that the said dose response data does not mentioned the threshold dose of the claimed compound. Also the compound 5 of the example 34 of the prior art shows 21% inhibition of tumor volume at 100 mg/kg daily dose ,where as the compound of example 3 of the claimed invention demonstrate 69% inhibition at 12.5mg/kg daily dose meaning thereby that the compound could have 8 times more activity than the compound 5 of the example 34 ,even this conclusion is unreliable in absence of any threshold doses data. Opponent also said that the applicant' assertion is wrong where it says that the example 3 of this application demonstrated 16 fold activity against the compound of the prior art ie; example 41 .As per the test data provided the compound shows 2.95 times binding affinity with the target enzyme compared with the affinity of compound of example 41 of the prior art, as per test (a) and 1.85 times binding affinity as measured by test (b).

Therefore opponent stated that (1) the claimed compound do not possess any surprising properties compared to the properties of the closest compound specifically disclosed in the prior art and the said comparative test data does not support the presence of inventive step. (2) the additional Declaration no. II of Mr. J R Woodburn dated January 5 1995,where the dosage in respect of compound 5 of example 34, in mg per kg of body weight has been reported. This additional activity data considers the activity of said compound 5 of the example 34 in isolation and therefore can not be substituted for the comparative data vis-à-vis closest prior art and therefore does not help in establishing the applicant's claim of inventive step and is not a comparative test data.(c) the dose response furnished by the applicant in respect of the compound5 of example 34 of the prior art is not persuasive because threshold –dose data has not been provided.

The applicant submitted that the three criteria for selection patent mentioned by the opponent i.e. (1) the scope of the selected species should be small as compared to that of the earlier patent (2) selected sub species should be sufficiently removed from the preferred aspect of the earlier invention ;and (3)selected sub species should have peculiar properties ,applicant submitted that all these criteria have been met. With regard to criteria (1), the R_1 group in EP/0566226 shows that 110 generic groups are mentioned and these may be located at 5,6,7 and 8-positions on the quinazoline ring whereas the number of generic substituent listed for the R_1 group at 6^{th} position in original claim 1 of the present application are only 11 and generic substituent listed at R_3 group at the 7^{th} position is only one .Similarly R_2 group in exhibit-1 shows13 generic groups whereas generic groups listed for R_2 group in original claims of the present invention is only 3.Hence the scope of the selected sub –species is indeed small compared to that of earlier patent application. With regard to criteria(2) , page 4,line 7-11 of the present application mentions that the invention is concerned with quinazoline compounds which bears at the 4^{th} position an aniline substituent and which also bears an alkoxy substituent at the 7^{th} position and a dialkylaminoalkoxy at the 6^{th} position. In EP/0566226 claim 6 provides a list of (R_1) groups . Substituents are present as a single 6 or 7 positions or as a pair of substituents at the 6^{th} and 7^{th} positions. there is a list of 37 possibilities , none of these mentions a group at 6^{th} position that falls within the generic term ‘dialkylaminoalkoxy. In claim 5 of the said exhibit provides that R_1 is to be located at 6 or 7^{th} position. There is a list of 73 possibilities just 5 of which falls within the generic term as a dialkylaminoalkoxy group. There is no disclosure of a quinazoline compounds which bears a ‘dialkylaminoalkoxy’ at the 6^{th} position and also bears an alkoxy group at 7^{th} position . Hence the present invention is sufficiently removed from the preferred aspect of the earlier invention . With regard to criteria (3) we submit that the data discussed above establish that the selected sub species do possess the peculiar property of enhanced efficacy in vivo.

The applicant strongly refuted the allegation of the opponent that the closest prior art have been selected erroneously. Due attention has been paid that there are major similarities in the structure of the prior art compounds and representative compound of the present invention. It has been found by the applicant that presence of basic group at 6th position of the quinazoline ring improves the physicochemical properties. Representative compounds of the present invention contain basic group at 6th position and the representative compounds of the prior art also contains basic group at the 6th position, whereas the compound 5 of the example 34 of the prior art has a methoxy substituent at the 6th position which does not possess such a basic group, and therefore not considered to be most suitable prior art compound. Applicant admitted that in the representative compound selected from the prior art has methoxy group at the 6th position of the quinazoline ring whereas the representative compound of the present invention the methoxy substituent is located at 7th position. Applicant also admitted that the representative compound of the present invention ,as well as the compound 5 of the example 34 , contains 3'-chloro-4'-fluoroanilino group at the 4-position of the quinazoline ring whereas the representative compound of the prior art selected for comparison have 3-methylanilino group at the 4th position of the quinazoline ring. However applicant asserts that ,as the compound 5 of the example 34 of the prior art does not contain a basic group at the 6th position which makes important contribution to the properties and activity of the compound, therefore ,not considered as most suitable prior art compound and submitted that the allegation of the opponent that compounds of example 26,41 and 64 are not representative of the closest prior art , would not be properly supportable.

Applicant invited the attention of the tribunal to wards the additional data for compound 5 of the example 34 which was provided to USPTO dated 5th june,1995 by J R Woodburn .Said compound was tested for activity against A-431 Tumor Fragments grown as xenografts in athymic nude mice. At a test dose of 200mg/kg orally per day said compound no. 5,within example 34 , gave rise to 30% inhibition of Tumor growth., the activity of which is no more better than the

prior art compounds of example 41 and 64, which gave 40% and 48% inhibition of Tumor growth respectively at a test dose of 200 mg/kg oral dose. The applicant submitted that the said compound no. 5 within example 34 is not a compound of better activity than the compounds of example 26, 41 and 64 of the prior art chosen by the applicant for comparison. Therefore the compounds chosen for comparison are appropriate and the comparative data establish that the present invention does involve an inventive step.

Not an invention

The opponent submitted that the clamed invention is neither novel and nor does involve an inventive step over the prior art . The alleged invention is not an "invention" within the meaning of section 2(1) (j a) of the Patent Act ,1970 , being devoid of novelty and inventive step as according to the definition of inventive step ,the invention should be a technical advancement over the prior art or it should show economical significance or both and it should not be obvious to a person skilled in the art .

The opponent also insisted that the instant invention do not meet the criteria laid down in section 2 (1) (l) and is not a new invention as the claimed invention has already been anticipated by use or publication, has been used before the filing date of the alleged invention in India and elsewhere. The opponent submitted that the subject matter of the claimed invention has clearly fallen in public domain in the form of publication of D1 , which was part of the state of the art on the alleged priority date of the claimed invention.

The applicant argued that the opponent allegation that the present invention does not meet the requirements of section 2 (1) (ja) and section 2 (1) (l) of the Patents Act . The argument lack any merit, in view of what have been submitted above that the claimed invention are novel and inventive.

Prior public use/prior knowledge

The opponent submitted that the cited document exhibit 1 has been in public domain prior to the date of the application under opposition and therefore forms the prior public knowledge. The opponent submitted that the process of the

alleged invention has been used in India and elsewhere and therefore the ground of prior public use/ prior public knowledge is established.

The applicant strongly refuted the allegation that the invention of he present invention is disclosed in exhibit 1, and contended that the opponent's allegation is without any merit, Also the opponent's allegation that the process aspects of the present invention have been in public use in India and elsewhere before the priority date of the present patent application. The applicant submitted that ,since the subject matter of claim 1 of the present invention is novel so is the process of preparing the said subject matter. The applicant requested the Tribunal to direct the opponent to provide evidence of the prior public useof a process for making the novel compounds of the present invention and submitted that in absence of such evidence the ground of opposition on prior public use, be rejected.

Not patentable invention (section 3(d))

The opponent submitted that mere discovery of a new form of a known substance which does not result in enhancement of known efficacy of the substance or mere discovery of any new property or new use of a known substance or of the mere use of known process results in a new product or employ at least one new reactants is not patentable under this Act.

The opponent states that the claim 1 of the exhibt-1covers the compounds disclosed in the alleged invention and its pharmaceutically acceptable salts whereas claim 14 specifically claims 'gefitnib' and claim 15 covers its hydrochloride salts while page 13 of specification of impugned application discloses *dihydrochloride salt in addition to hydrochloride salt of gefitinb.* Line 30-37 of the Exhibit -1 discloses different acceptable salt of quinazoline derivative, last paragraph of page 7 of the impugned application provides "*A suitable pharmaceutically acceptable salt of quinazolne derivative of the invention is ,for example, acid addition salt of a qunazoline derivative ……..for example ….. hydrochloric, hydrobromic, ,sulphuric ,phosphoric ……"*. sixth paragraph of page 5 of Exhibit -1 states that the said qiinazoline derivative could be prepared by conventional procedure. The opponent submitted that there is no

question of mere discovery of a new form of a known substance or the mere discovery of any new property or new use of a known substance because gefitinib , its salt , their use as anti tumor, are clearly taught in the prior art. Further to show enhanced efficacy over the known substance the applicant in this case, has only provided ED50 values, whereas the proper parameter to judge the efficacy of a molecule is therapeutic index (TI) which is the ratio of LD50/ED50.The higher the TI ,better the drug. The applicant has failed to provide the LD 50 values to able to show the TI to be low .

The opponent further submitted that it is admitted in the document submitted to the CDER for New Drug Approval of 'Gefitinib' that *US 545710 covers the formulation, composition and/or method of use of IRESSA (gefitinib) tablets* .It is submitted that Us 457105 is an US equivalent of Exhibit -1. The invention claimed by the applicant is only an obvious extension of the knowledge available in the art and lack inventive merit. Therefore it is evident from the above submission that the applicant failed to satisfy the condition set out by section 3(d)and liable to be rejected being not patentable under the Act.

The applicant countered that the allegation of the opponent's argument , "*that the present invention does not meet the requirement of section 3(d),that a claim that embraces their pharmaceutically acceptable salts merely amounts to a salt of known compound*", lacks any merit as the compounds clamed are novel and inventive in view of what have been submitted above. The applicant submitted that the opponent is trying to mislead the Honourable Tribunal by confusing *'what is being encompassed within the claims of a patent' with 'what is disclosed within a patent application*. US patent no . 54,57,105 is an equivalent of EPA 0566226 (Exhibit-1). Iressa (Gefitinib) is encompassed within certain of the patent claims of US Patent no, 54,57,105 ,but the compound is not disclosed therein. The fact that the compound is encompassed within the claim, led the applicants, to list US patent no, 54,57,105 in their dealing with the Regulatory Authorities. Since the claimed invention has not been taught by the cited prior art and is novel and inventive therefore does not fall within the ambit of Section 3(d). of the Act.

Decision

On the basis of the arguments and evidence given by both parties I am of the opinion that the basic skeleton of the prior art compound and the present invention are same. The prior art also teaches chloro fluoro substituent in the aniline attached to the 4th position of the quinozoline molecule and a methoxy group at the 7th position of the quinozoline. But I find that none of the compound disclosed in the prior art is identical to the compound disclosed or claimed in the proposed claim-1 in the present application with respect to the 3, 4 & 7th position of the quinozoline molecule. The prior art does not teach exclusively the claimed compound. Therefore the said selected compound of the present invention is novel over the prior art.

Regarding lack of inventive step/obviousness ,it is well settled , that the law of selection is more concerned with anticipation rather than obviousness. However in the **Ranbaxy UK Limited and Arrow Generics Limited v. Warner Lambert Co.In the High Court of Justice,Chancery Division ,Patent court,the judgement ordered by The Honourable Mr Justice Pumfrey states that obviousness only become relevant if the latter patent is not anticipated. The groung of obviousness and lack of inventive step was argued by both the parties without prejudice to their submission on anticipation.** In the present case I feel justified to address the issue of lack of inventive step/obviousness.

An additional data for the said compound 5 of the example 34 in the form of a Declaration II of Mr. Woodburn has been provided by the applicant in this case. But the applicant's argument is not strengthened by the declaration that '*the inventive strength of the instant invention is based on the surprisingly low ED50 values which translate to the compounds having at least four folds and in some cases 16 fold potency as compared to the compounds of the prior ar*t.' The declaration furnished, does not provide any ED50 values of those said tested

compounds ,rather it provides the percentage inhibition of the tumor growth at predetermined dosage levels. I therefore do not find the evidential value of the said declaration to be convincing at all in relation to the documents and arguments already on record.

Regarding closest prior art issue I find, that in the present application following substitution has been claimed

(a) 3' &4' position; could be chloro or fluoro

(b) 7th position of quinozoline ring; Methoxy and

(c) 6th position of the quinozoline ring; a basic group.

The compound 5 of the example 34of the prior art reference has the same substituent at the 3',4' and at the 7th position of the quinozoline ring but different at 6th position ,whereas the compared compound of example 64 has a basic group at 6th position but substituent at 3',4' and at 7th position are different and in compounds of example 26 and 41 none of the above substituents in exactly on the same place as claimed in the present invention

The opponent relied upon the European Board of Appeal decision T 181/182 which held that '*an effect which may be said to be unexpected, can be regarded as an indication of inventive step*; *where comparative test are submitted as evidence of this, there must be the closest possible structure approximation, in a comparable type of use-to the subject matter of the invention'* .In the paragraph 5 of the same decision it states;

"To be relevant, such comparative test must meet certain criteria. These includes the choice of a compound disclosed in the application and of comparative substance taken from the state of the art; at the same time, the pair being compared should possess maximum similarity with regard to structure and application. Given the similar properties to be expected in view of the structural similarity of two substances, evidence of an abrupt improvement can be regarded as unexpected .The greater the structural difference between the compound being compared, the less unexpected are any difference in their effects. So if a meaningful statement is to be made in order to render an inventive step possible,

compounds having a maximum structural resemblance must be compared with one another".

Following the above basis, I find that the compound of Table 3 within example 34 comes structurally closure to the claimed compounds than any of the compounds of example 26,41 and 64 of the prior art in disclosing the same 3',4' substituent and 7- methoxy substituent .Therefore compound 5 within example 34 is the closest prior art compound, which would require minimum structural modification in order to reach the compound claimed in the present invention.

The requirement for a comparison with the closest prior art is based on the principle of the structural dependence of the properties of the substance i.e. on the fact that these properties reflect the structure of the substances.

Therefore it is very difficult to accept the applicant's claim of 16 fold potency of the compound of the present invention against the compound disclosed in the prior art because the comparison provided is not against the closest prior art. Even if I agree with the arguments of the applicant that the basic group at the 6^{th} position makes an important contribution to the properties and activities of the claimed compound the compound 5 of the table III within example 34 of the prior art , should have been used as comparative test compound, as the said compound 5 of Table III within example 34 of the prior art differs from the claimed compound in the presence of basic group at the 6^{th} position. This could have provided a suitable platform for the demonstration of the surprising effect of the claimed compound vis-a vis the said example compound 5 of the example 34 (Table 3). This could have proved that the surprising or the unexpected properties of the claimed compound is associated with a basic group at 6^{th} position of the ring .In absence of any comparative test data provided vis-a –vis compound 5 of example 34of the prior art, the applicant's claim that the compound of the present invention are 4 to 16 times potent as compared to the prior art reference is not very convincing.

I do not agree with the contention of the applicant that the compound 5 of the example 34 of the prior art EP/0566226 was not considered for comparative test data as the same compound did not contain a basic group. The technical

advancement could only be demonstrated by looking forward from the prior art to the claimed invention and not the other way around .The proper approach to demonstrate the inventive step is to move forward from the prior art i.e. the comparative test data should have been provided vis-à-vis the structurally closest compound of the prior art which in my opinion is the compound 5 of example 34 of EP/0566226 , because this compound of the prior art differ from the claimed compound only in the presence of the basic group ,which the applicant admitted, play an important role in the activity of the claimed compound.

I agree with the opponent's contention that for the demonstration of 'technical advancement 'must be shown to have been achieved by a claimed invention vis-a vis the prior art by way of demonstrating the presence of an unexpected effect over the closest prior art. Any comparative test data provided against said compound 5 of example 34 could have highlighted the criticality of the 'basic group' in achieving an enhanced activity, which could have formed the basis for the invention. Therefore, I have no doubt that the applicant has failed to provide comparative test data vis-a vis the structurally closed compound of the prior art.

However, on considering the comparative test data provided in the statement dated 21st January, 1997 by Mr. J.R.Woodburn I found that the test data in respect of only 23 compounds out of 60 compounds of the claimed scope of the present invention has been provided. Applicant has therefore failed to prove the surprising effect over the entire claimed scope .The arguments of the applicant appears valid that, the IC_{50} values which is 'minimum inhibitory concentration of the compound required to inhibit 50% of the test target' is not a very correct parameter to test the efficacy of the compound, as it may be possible that the highly active compound may also be highly toxic. More reliable parameter for testing efficacy of a compound is the therapeutic index. The lower the therapeutic index better would be its efficacy.

Even the IC_{50} value provided by the applicant shows that except the compounds of the example1, 3,4,6and 9all the other compounds are less active than the prior art compound of example 41 chosen by the applicant. Among them

the most active compound is 1.45 to 2.9 times potent than the prior art compound. This variation of 1.45 to 2.9 times in such experimentation is very much expected. Therefore variation in a selection of a class with in the prior art disclosure of broad generic class of compounds showing 2.9 times activity is not an, unexpected or surprising activity.

Similarly in test (b) I found that claimed compounds vis-à-vis alleged closed prior art compound of example 41 shows that most of the compound of the present application shows similar activity compared to the most potent compound of the prior art. Among the most active compounds of the claimed invention, compounds of example 1,4, 6 and 9 shows approximately 7.4 times as active as the compound of the example 41 of the prior art. But the expected variation in the activities of the compounds especially when the prior art discloses a large class of compounds and a selection of a class within the prior art shows only about 7.4 times which can not be termed as unexpected or surprising.

The applicant has also submitted a dose –response relationship data as compared to the prior art compounds. It is observed that the compound of example 41 and 64 of the prior art shows 40 and 48% inhibition of tumor at 200 mg/kg/day oral dose. Majority of the compounds of the present invention shows comparable result at oral dose of 50 mg/kg/day. This shows that these compounds are at least 4 times more potent than the prior art compound of example 41 & 64. I agree with the submission of the opponent that the randomly selected doses data with incomparable inhibition of tumor volumes, can not be used for comparing the activity the claimed compounds .Comparison should be made on the basis of threshold dosage,which has not been provided.Compound 5 of the example 34 ,as per the table I of the declaration oII of Mr. J.R.Woodburn,shows21% inhibition of tumor volume at 100 mg/kg/day oral dose. The most active compound as alleged by the applicant i.e. the compound of example 3 demonstrates 69%inhibition. This means that the compound could have 8 times more activity than the prior art compound 5 of example 34, but the same appears unreliable in absence of threshold dosage data.

In view of above I find that, the surprising effect that the applicant alleged by comparing IC_{50} values instead of therapeutic index value, does not qualify for claiming inventive step.

The above findings lead me to conclude that the applicant has not made the proper demonstration of the inventive step because:

(a) Comparative test data provided vide statement dated January 21,1997 by Mr. Woodburn fails to substantiate that the claimed invention in the present application possess surprising properties compared to the closest compound that were specifically disclosed with in the prior art reference.

(b) The applicant's contention, that the compound of example 1 and 3 of the present invention are 16 fold more potent than the compounds of example 41 and 64 of the prior art because these compounds of the example 41 and 64 do not form the closest prior art. Therefore the claims of 16 folds potency vis-à-vis closest prior art are not persuasive.

(c) An invention is deemed to involve an inventive step, if it involves technical advancement and is not obvious to a person skilled in the art. However I find that the requirement of the technical advancement has not been demonstrated from the view point of 'looking forward' from the structurally closed compound of the prior art, as it is evident from the absence of any evidence of surprising potency vis – a vis closest prior art compound.

(d) The applicant's contention that the basic group substituent at the 6^{th} position of the quinozoline ring confers preferred physico-chemical properties to the compounds of the claimed invention. The comparative test data provided by the applicant does not establish the contention that 'the selective positioning of the basic group is actually responsible for the surprising potency of the claimed compounds'. The compounds of the example 26 , 41 and 64 of the prior art have the different substitution at the 3,4 position of the anilino group and 7^{th} position of the quinazoline ring, than the substitution in the claimed compounds. Therefore the

comparative test data and the statement of Woodburn does not establish the superior potency that resides in the selective positioning of the basic group only.

(e) I can not agree with the contention of the applicant that the compound 5 of example 34 of the prior art is not suitable comparison because this compound does not contain the basic group. Selection of the closest prior art compound is an objective determination based on the structural similarity between the chosen compounds and the claimed compound and does not depend on the suitability of the chosen compound for comparison. Compound 5 of the example 34 of the prior art has a methoxy substituent at the 6^{th} and 7tjh position while having the claimed 3' chloro-4' fluoro substitution on the anilino group and does not possess the basic group. This compound therefore constituted the closest prior art and any surprising potency observed vis –a – vis compound , could have convincingly demonstrated the criticality of the selective positioning of the basic group for achieving the desired superior physico -chemical properties.

My finding of lack of inventive step is further strengthened by the disclosure of the claimed compounds within the preferred portion of the invention disclosed in the prior art. In assessing the obviousness of the claimed selection invention vis-à-vis the teaching of the prior published document, it is important to take into account whether the 'claimed invention' is far removed from the preferred aspect of the invention disclosed in the prior art published document;

(a) On page 17 of EP 0566226 B1,at line3-20, describes particular novel compounds of the invention disclosed. Line 3 teaches the preferably "m" may be 1,2 or 3. Line 4 lists (1-4C)alkoxy as preferred substituent and further preferred substituent for R1 disclosed are:

Line 11, di (1-4C) alkyl] amino- (2-4C) alkoxy which covers 2-dimethyl amino ethoxy ,2-diethyl amino ethoxy, 3-dimethyl amino propoxy,and 3-diethyl amino propoxy from the list of the substituent in the present invention.

Line 13- Piperidino (2-4C) alkoxy,which covers 2-piperidino ethoxy and3-piperidino propoxy from the list of substituents of the present invention.

Line 13 –morpholino (2-4C) alkoxy, which covers 2-morpholino ethoxy and 3-morpholino propoxy from the list of substituents in the present invention

Line 13 –piperazin-1-yl- (2-4C)alkoxy ,which covers 2-(4-methyl piperazin-1-yl)ethoxy from the list of substituents in the present invention.

Line 30-32 –teaches that n is preferably 1 or 2 and each R2 is independently halogen , trifluoromethyl or (1-4C) alkyl.

In another preferred aspect of the prior art on page 19 ,line 8-20, I find that the groups 3',4' dichloro and 3'-chloro,4'-fluoro are clearly the preferred substituents for R2. The same paragraph also lists 7-methoxy as the preferred substituent at the 7th position of the quinazoline ring.

Therefore I find that the compounds claimed in the application under opposition fall within the novel preferred aspect of the invention disclosed in the broad disclosure of the prior art EP 0566226 B1.It can be seen from the present invention that it claimed more limited generic class consisting much fewer compounds as compared to broad generic class of compounds disclosed in the broadest scope of the prior art reference. The limited number of compounds covered by the preferred formula in combination with the fact that the preferred number of substituents is low at 3'&4' position, as it is evidenced by the preferred definition of R2 and the ring position were limited to only four positions namely 3',4' position of the aniline ring and 6th &7th position at the quinazoline ring where possible substitution could have taken place and a large unchanged structural nucleus lead me to find that the reference EP 0566226 ,sufficiently motivates a person skilled in the art ,looking for further quinazoline derivative having higher activity , to investigate within the compounds disclosed in the preferred part of the prior art reference and in doing so he would arrive at the compound claimed in the present application under opposition. I don't have any doubt that the person skilled in the art would have any difficulties, in preparing at least the compounds disclosed in the 'preferred embodiment' of the compounds disclosed in the prior art reference. I find that the compounds claimed in the instant

invention as a class are sufficiently motivated and therefore obvious over the prior art reference, because a person skilled in the art looking to obtain further quinazoline derivatives could prefer to begin from the most preferred embodiment of the prior art disclosure and would not have to conduct undue research and experimentation to arrive at the particular combination of the functional group encompassed by the present application starting with the preferred compounds of the prior art.

To summarize the findings on the obviousness I conclude that it is easy for a person skilled in the art to reach the compounds claimed in the application under opposition using the disclosure of prior reference cited by the opposition because;

(a)The number of compounds covered by the preferred formula on page 17 of EP 066226 is limited.

(b) The preferred number of substituents are low at the 3' & 4' position as evidenced by the preferred definition of R2 in the particularly preferred embodiment of the prior reference.

(c) Ring positions were limited to four position only i.e.3' & 4' position on the aniline attached to the quinazoline ring and 6^{th} & 7^{th} position on the quinazoline ring. Out of which 3' &4' position having been frozen for (fluorine, chlorine) or (chlorine, fluorine) and methoxy group at 7^{th} position , only 6^{th} position remains , where possible substitution could take place thereby reducing the choice available to a skilled person setting out to interpret the prior evidence.

(d) A large unchanging structural nucleus in the claimed compounds as well as the compounds in the prior art.

Therefore in absence of any conclusive evidence regarding the technical advancement offered by the claimed compounds, in absence of comparative test provided with the closest prior art and further in view of the implicit and motivating disclosure of the claimed compounds within the preferred part of the prior art reference I conclude that the invention claimed in the present invention under opposition, does not involve an inventive step and is obvious to arrive at, with respect to the prior art.

In respect of prior public knowledge/ prior public use, I found above that the invention claimed in the present application is novel but the opponent's argument , that the state of the art constitute not only the explicit teachings of the prior publish documents but also modification thereof, obvious to a person skilled in the art, does not appears to be very persuasive. The applicant has also not denied that a substantial portion of the claimed invention is 'encompassed' but not disclosed within the prior art cited by the opponent. The opposition also has drawn the attention to the NDA application number 21—399, which concerned IRESSA (Gefitinib) tablets, which is also covered under the present application. Paragraph A (7) (b) states that **"***US Patent No.5 457 10 5 contains drug substance claims, pharmaceutical composition claims and method of use claims"* Further a declaration on behalf of the applicant states that "*The undersigned declares that US Patent number 54,57,104 covers the formulation ,composition and /or method of use of IRESSA (Gefitinib) tablets. This product is the subject of this new drug application for which approval is being sought."*

The fact is 'gefitinib' is encompassed within certain of the patent claims of the US patent/ 547105 and listed the said US patent in their dealing with the US Regulatory Authorities. But as I have found above, that in particular Gefitinib is not disclosed in the US patent / 5457105. The opponent argument on the basis of above evidence is not found persuasive and since I found that the compounds of the present invention are novel over the prior art, the compounds of the present invention were not in prior public knowledge on the date of filing of this application. Also the opponent has not submitted any conclusive evidence before this tribunal regarding prior public use of the compounds of the present invention, I shall agree with the applicant's argument that the compounds of the present invention are not in public use.

Regarding patent ability under section 3(d) , I find that the test data provided by the applicant does not substantiate the applicant's claim of significant enhanced potency residing in the selection of a basic group at 6-position of the quinazoline ring. The applicant has attempted to claim enhanced efficacy by demonstrating that the compounds of the claimed invention possess 4

to 16 fold potency compared to the compounds of the prior art. Based on my findings under the ground of obviousness and lack of inventive step wherein I concluded that the claim of the applicant that the compounds of the present invention are 4 to 16 times more potent than the prior art compounds, are not persuasive, I conclude that all the compounds claimed in the present invention do not significantly differ in efficacy compared to the prior art which is the explicit requirement under section 3(d) and therefore is not patentable under section 3(d) of the Patent Act.

Again under the ground of 'not an invention ' within section 2(1)(j), I rely on my earlier findings. As the invention claimed in the present invention is obvious and does not involve an inventive step over the disclosure of EP 0566226, I find that the claimed invention is not an invention within section 2(1)(j) of the Patent Act 1970.

In view of my findings in the preceding paragraphs, I conclude that the present invention as claimed in revised claim 1 to 12 of the application number 841/DEL/1996 is;

(a) Novel over the prior art disclosure of EP 0566226

(b) Obvious and does not involve an inventive step over the prior art EP 0566226;

(c) Not an invention within the meaning of section 2(1)(j) of the Patent Act 1970;

(d) Is not patentable inventionwithin the meaning of section 3(d) of the Patents (Amendment) Act ;

On the basis of the above findings and the circumstances of the case I refuse to proceed with the application number 841/DEL/1996 for grant of patent.

The applicant after the conclusion of the arguments in the hearing, submitted a modified proposal of claims, changing a major part of claim 1 and all the other 10 claims and proposed the following three claims.

Claim (1) –The quinazoline derivative: 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline ;or a pharmaceutically acceptable acid addition salt thereof.

Claim (2) –The hydrochloride salt of the quinazoline derivative as claimed in claim 1 .

Claim (3) – A pharmaceutical composition which comprises the quinazoline derivative 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3morpholinopropoxy)quinazoline ;or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutically acceptable diluents or carrier.

As my opinion given in preceding pages regarding claims 1 to 12 of the amended claims includes the proposed set of claims as above, submitted by the applicant, therefore these claims are again refused on the same grounds

The application stands disposed with no cost to either party..

Dated this, the day of 30th august,2007

(S.K. Roy)

Assistant Controller of Patents & Designs.

Copy to:

1. M/s Remfry & Sagar,
   Remfry House, millennium Plaza Sector – 27,
   Gurgaon – 122 002.

2. M/s Majumdar & Co.
   5, Harish Mukherjee Road,
   Kolkata – 700 025.