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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 Natco Pharma Ltd., India ..... The Opponent

Hearing held on 18th July, 2006

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 Natco Pharma Ltd. on 9th August 2005 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 6th March, 2006 with a request for hearing u/r 55 of the Patents (Amendment) Act, 2005. Hearing was fixed on july18th,2006. both the party to the opposition attended the hearing on 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) Prior use/Publically 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)
(8) Convention application mentioned within 12 months 25(1)(i)

and submitted following supporting documents alongwith the statement ;

(1) copy of the official journal dated. 11.3.2005 (2)Patent document EPO 566226 (3)Patent document US 5457105 (4)Patent document US 5616582 (5) copy of the Electronic orange book reference gefitinib (6) Copy of Patent priority listing (7) Handout on Markush structure on Patent (8) British High Court decision on Merck Patent.

Applicant in the reply statement submitted four supporting documents including one evidence (1) Test evidence by Dr. Tracey Briant (2) Copy of Form 3 filing (3) Copy of priority document (4) an additional test sample report.

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.

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

For raising the grounds of anticipation opponent relied upon the document EP/566226 and its equivalent US/5457105. They submitted that amended claim 1 of the application is not novel on the face of US/5457105 (hereinafter D_1), which is equivalent to and has the same contents as EP/566226 published on October 20, 1993. The opponent compared the substitutents at $R1_1$ & R^2, position of the claim 1 of the application with disclosure US/5457105 (D 1) wherein in the R^2 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 R^2 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_1. At R_1 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-peperideno ethoxy & 3-pepierdino 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_1 may be selected from 2 (pyrrolidin-1-yl) ethoxy, 2-(pyrrolidin-1-yl) propoxy, 2(Imidazole-1-yl) propoxy, 2(di-(2-methoxy ethyl) amino] ethoxy and 3-morpholino-2-hydroxy propoxy are novel over prior art document D_1. Therefore substantial portion of the amended claims of the opposed application except the above said novel position 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 6^{th} 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 6^{th} position (column 8 line 40). Claim 5 and claim 7 of the present invention are novel over prior art as the substituent at 6^{th} 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 D1.

The process claim 11 is also not novel on the face of column 15 of D1 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 application 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 D1). Also the pharmaceutical composition is also not novel on the face of D1. The opponent argued that the said claim is directed to known quinozoline derivative (anticipated by D1) in association with conventional pharmaceutical feature that render the claimed subject matter not novel over document D1.

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 classIn 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 must favoured embodiment disclosed in the prior art. Therefore claimed invention is clearly anticipated by the prior art.

Opponent further argued that the law relating to selection patent has been authoritatively stated by the House of Loards 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 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 5457105, 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.5457105 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 5457105 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 quinozoline 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 embrances 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 halogeno amino 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 has been 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 judgement from fleet Street Report 1982 E.I. Dupoint 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 judgement 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.

In respect of ground of lack of inventive step / obviousness the opponent argued that the claimed compound of the alleged invention are clearly obvious and devoid of inventive step compared to the compound of document D1. To substantiate it arguments opponent referred to the 2nd Paragraph of page 20 of the present specification which states that the compound of the alleged invention possess anti-proliferative properties such as anti cancer which are believed to arise from their class 1 receptor tyrosine kynase inhibitory activity.

The document DI discloses vide column 2, line 20-26...." We have now found that certain quinozoline derivatives posses anticancer properties which are believed to arise from their receptor tyrosine kinase inhibitory properties." The opponent states that the claimed compound possess the same anti-proliferative activity which similarly arises from the receptor tyrosine kinase inhibitory properties of the compound disclosed in D1. The document D1 discloses at several places that anti cancer properties are expected of the compounds disclosed their in an verification of the same properties are purportedly by made out in the opposed application which is clearly & strongly motivated by the teaching of the prior art D1. Therefore the alleged invention is an attempt by the applicant to create a monopoly over the compound which is clearly in public domain and therefore should be rejected.

Opponent stated that the comparative test data furnished by Mr. J.R. Woodburn to show enhanced efficacy is not appropriate as the prior art chosen for comparative test are not the closet prior art. In this regard opponent has referred to **a decision T 730/96 of the European Technical Board of Appeal** which has laid down the criteria that should be adhered to in order to identify the closest prior art for the assessment of the inventiveness.

The criteria are that a closest prior art is a prior art:

1. ***disclosing the same subject matter conceived for the same purpose as the claimed invention and,***
2. ***having the most relevant technical feature in common i.e. requiring the minimum of structural modification.***

The decision further stated ***"it is the established jurisprudence of the Boards of Appeal that, to be relevant comparative tests must meet certain criteria. These include the choice of a compound disclosed in the patent in suit and of a comparative compound taken from the state of the art; at the same time, the pair being compared should possess maximum structural similarly. This comparative test must be carried out in respect of the closest state of art".***

The opponent argued that in the present care as per the claim 1, the **essential feature** of the invention are 7-methoxy substitutent in the quinazoline ring and 3 and 4 substitutions on the anilin ring selected from flourine or chlorine.

Example 1-4 have at least these minimum technical feature in common (ie all the compounds possess 7-methoxy substituents and possess 3'-chloro 4'-fluoro substituent on the aniline ring) and therefore are the appropriate compound for comparison where as the applicant has conveniently selected from the state of art Example 26, 41 & 64 as closest prior art for comparison where in Example 26 contains dimethyl amino ethoxy at the 6th position and 3 methyl instead of 3,4, dihalo. Similarly in example 41 no halogen atom was found in the aniline ring and at 7th position, it is morpholino propoxy istead of methoxy. In example 64 at the 7th position of the quinozoline there is only H instead of methoxy and no halogen in the aniline ring. Therefore none of the selected compounds from the state of art has 7 methoxy group in the quinozoline ring and 3-4 dihalo substitutents more specifically 3-chloro-4-fluoro substitutents at the aniline ring. These compounds therefore do not meet the essential feature of the present invention and in therefore not the closest prior art which has been taken for comparison.

Therefore the 16 fold efficacy claimed by the applicant over the prior art compound which are not closest prior art is merely an eyewash.The opponent stated thet the compound 5 of example 34 ,Table III of the prior art, whose structure reveals to be the closest prior art because it provides methoxy group at 7th position and 3'-chloro 4'-fluoro substituent on the aniline,met both the essential features of the claimed invention and therefore indeed the closest prior art.

Opponent further relied upon the decision T 181/82 of the European Technical Board of Appeal in this regard which states

"However, an effect demonstrated by means of comparative test can be regarded as an indication of inventive step; the only test suitable for this are those which are concerned with the structural closeness to the

invention, because it is only here that the factor of unexpectedness is to be sought.

The requirement for a comparison with the closest prior art is based on the principle of the structural dependence of the properties of chemical substances i.e. on the fact that these properties reflect the structure of the substances. Given the similar properties to be expected in view of the structural similarly of two substances, evidence of the abrupt improvement can be regarded as unexpected. The greater the structural difference between the compounds 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 plausible, compounds having a maximum structural resemblance must be compared with one another".

Therefore there can be no denial that the compound 5 was also specifically disclosed in the prior art but conveniently ignored for comparisons. The claimed compound does not possess any surprising property compared to the properties of the closest compound those were specifically disclosed in the prior art. Therefore the comparative test data doesn't any way support the presence of inventive step. In other words the claim of the applicant of significant efficacy in claimed compounds over the known prior art does not hold good. The opponent also drawn the attention to page 5 of the applicant's specification which provides that there is no disclosure in the prior art of the quinozoline derivative that possess an aniline substitutent at 4^{th} position, an alkoxy substitutent at 7^{th} position and a dialkylaminoalkoxy substitutent at 6^{th} position. Opponent argued that all the basic structure of the compounds are disclosed in the prior art claim, text and example which provides 4-anilino substituent., alkoxy substituent at the 7^{th} position at different places ,reference of which has already been mentioned under anticipation ground and 6-amino substituent has also been specifically taught in D1

In respect of lack of inventiveness' the applicant strongly resisted the allegation of the opponent that "the present invention has already been disclosed in the earlier patent where it is mentioned that the quinazoline derivatives defined

in the invention are expected to have anticancer properties" and stated that they doesn't deny the quinazoline derivative are expected to have anticancer properties but the instant invention shows surprisingly good potency in the invention compared to the prior art which forms the basis of the inventive step. Particularly compounds of example 1 & 3 of the present invention have established the therapeutic efficacy upto 16 fold better than the previously claimed compound and the same is evidenced by the comparative date submitted by Mr. J.R. Woodburn. It is therefore evident from our submission that the present invention does involve a technical advancement and it would not have been obvious to a person skilled in the art to arrive at the specific combination of functional groups at specific position on the quinozoline ring.

The applicant also resisted the opponent allegation that the dosage range mentioned in the data provided in the present application falls within the range mentioned in the prior art and hence "No technical advancement" and stated the dosage is dependent on variety of factors like age, sex weight etc. therefore cannot be made a basis for comparison.

In the comparative data submitted by Mr. Woodburn was given is ED 50 form and not in dosage form which refers to the dosage of the drug by which 50% inhibition of the malignant tissue is achieved. Once it is proved that the compound is more efficacious the dosage will automatically come down, since the dosage is dependent upon efficacy, further the opponent has shown the dosage range in the prior art approximately 0.1 to 100 mg/kg preferably 1-50 mg/kg and in the present case approximately 0.1 to 200 mg/kg preferably 1-100 mg/kg but at the same time the present invention also mentions against compound of example 1 on daily dose of 1-20 mg/kg preferably 1-5 mg/kg is employed, clearly indicating the technical advancement for quinazoline derivative of example 1.

The applicant also resisted the opponents argument that example 1-4 of the present invention have been conveniently compared with the example 26, 41 & 64 of the prior art which can't be considered as the closest prior art structurally. And the applicant has willfully chosen structurally dissimilar compounds to

establish the enhanced activity and not compared with compound 5 of (Table 3) with the example 34 of the prior art document, which is structurally the closest. (Two substitutents are functionally and positionally same and they refer to a EPO board of appeal decision vide case No.T-0181/82-3.301). The applicant argued that the comparison have been made between the most representative compounds of the prior art vis-à-vis the most representative compounds of the present invention and therefore the opponent's allegation that compound of example 26, 41 and 64 are not close prior art is completely baseless and misleading. The applicant submitted in the written argument filed, though not argued at the hearing, that an important structural feature of the compound of the instant invention that conferred preferred physiochemical properties was a basic group substituent on the quinozoline ring. They submitted that the compounds of example 26, 41 and 64 of the prior references were selected for comparative testing because they too have the structural feature of a basic group wherein the compound 5 of Example 34 of the prior reference did not posses such basic substituent and therefore was not considered relevant for comparison.

In respect of prior public knowledge/prior public use,the opponent submitted that the prior art reference has already fallen in public domain and therefore formed part of the state of the art before the priority date of the instant invention.

The opponent drew attention to the NDA application Number 21-399,relating to IRESSA (gefitinib) tablets , paragraph A (7)(b) of the same document states

"US Patent No.5457,105 contains drug substance claims,pharmaceutical composition claims and method of use claims."

Further under paragraph A(7)(c) states:

The undersigned declares that US Patent No.5457,105 covers the formulation, composition and/or method of use of IRESSA (gefitinib) tablets. The product is the subject ofthis new drug application for which approval is being sought."

Above declaration clearly shows that the claimed invention is a mere attempt to reinvent the prior art and reclaim the knowledge which has already gone into the public knowledge prior to the priority date of the application under opposition.

Applicant also opposed the opponent's allegation that the present application is anticipated by prior public knowledge because in the NDA application for IRESSA (gefitinib) tablets the applicant has given declaration that US Patent No.5457105 covers the formulation, composition or method of use of IRESSA tablets, which demonstrates that the claimed invention is a mere attempt to reinvent and reclaim the knowledge which has already lapsed into the public domain. Applicant submitted that NDA was approved on May 5th, 2003 much after the date of filing of the present application on April 19th, 1996 and therefore it was not a prior public knowledge on the date of filing.

In respect of "Not an invention" the opponent argued that the claimed invention is neither novel nor does involve an inventive step over the prior art. Therefore the claimed invention is not an invention with in the meaning of Section 2 (1) (j) of the Patents Act,1970. The opponent further argued that the new invention under the Patents Act means ""any invention or technology which has not been anticipated by publication in any document or is used in the country or elsewhere in the world before the date of filing of the Patent application that means the subject matter has not fallen in the public domain or does not form part of the state of art". The present invention is not a new invention as the claimed invention has clearly been anticipated by use or publication, before the filing date of the alleged invention in India & elsewhere. The subject matter has clearly fallen in public domain in the form of publication of DI which has formed a part of the state of the art. Therefore claimed alleged invention is not an invention within the meaning of section 2[1(j)] of the Patents Act, 1970.

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 " , lack any merit , in view of what have been submitted above ,that the claimed invention are novel and inventive .

In respect of 'not patentable invention' the opponent argued that the claimed invention is not patentable under Section 3 (d) of the Patents Act ,1970 as it claimed compounds that are either anticipated by the prior art or are minor variants or derivatives of the prior art compounds and do not significantly differ in therapeutic efficacy over the compounds of the prior art. Section 3(d) states that the derivative of a known compounds are deemed to be the same substance unless the compounds differ significantly in efficacy in comparison to the known form of prior art. The comparative test data provided by the applicant do not hold water ,as the comparative test example chosen by the applicant do not represent the closest prior art. In the NDA application Which concerns the compound 'Iressa' tablet, wherein ,it stated in paragraph A(7)(b) clearly states that 'US Patent number 5 457 105 contains drug substance claims, pharmaceutical claims and method of use claims and further in paragraph A(7)(e),states, 'the undersigned declares that US Patent No. 5 457 105 covers the formulation ,composition and or method of use of 'Iressa' tablets. The product is the subject of this new drug application for which approval is being sought.' ,clearly demonstrate that 'Iressa ' is disclosed in the prior art because the prior art US 5 457 105 , can not claim Iressa until and unless it discloses that molecule. The applicant has failed to provide any therapeutic index data or any lethal dose data to prove any heightened efficacy of the claimed compound.

The applicant argued that the allegation of the opponent is baseless that "the claimed compounds are derivatives of the prior art compounds and do not significantly differ in therapeutic efficacy". The word derivatives are used merely to indicate that the claimed compounds` are based on the quinazoline ring and not in the sense that the quinazoline ring is derivatized to produce salt ,esters etc.The present invention is novel and is not a mere derivatization of a known substance, which has been arrived at after extensive research and development and therefore ,does not fall within the meaning of the exceptions listed in Section 3(d).

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 after the conclusion of the oral proceedings by the applicant depriving the opponent from making any counter arguments. Therefore such documents which has been submitted after the prosecution of the opposition proceedings including final hearing, in my opinion ,need not be taken on record for consideration . 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 6th position makes an important contribution to the properties and activities of the claimed compound ,the compound 5 of the table 3 within example 34 of the prior art should have been used as comparative test compound, as the said compound 5of Table 3 within example 34of the prior art differs from the claimed compound in the presence of basic group at the 6th 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 6th position of the ring .In absence of any test 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.

The above findings lead me to conclude that the proper demonstration of the inventive step has not been made by the applicant 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 is 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 of the compounds of the claimed invention. The comparative

test data provided by the applicant does not establish the contention of 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 and64 of the prior art have the different substitution at the 3,4 position of the phenylanilino group and 7th 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 34of 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 6th and 7th position while having the claimed 3' chloro-4' fluoro substitution on the anilino group but 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 that "m" may be preferably 1,2 or 3. Line 4 lists (1-4C) alkoxy as preferred substituent and further preferred substituent for R1 disclosed are:

Line11- di(1-4C)alkyl]amino-(2-4C)alkoxy which covers 2-dimethyl aminoethoxy ,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 7^{th} 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 6^{th} &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 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 it suffers from obvious and lack in inventive step over the prior art cited by the opponent. The opponent 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 within the prior art cited by the opponent but the compounds of the present invention are not specifically disclosed theirin. The opposition also 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 5457 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 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 066226, I find that the claimed invention does not fulfil all the requirements of a invention and therefore, 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 invention within 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.

Here It is pertinent to note that after the hearing of the case but before the decision could be issued another pre-grant opposition was filed by M/s G.M. Pharmaceuticals Ltd. On 21st November,2006 Therefore the decision on this opposition was kept in abeyance till the conclusion of the hearing of the second pre-grant opposition. The hearing of the said opposition held on. 21st March, 2007 . This decision is being issued along with the decision on the second pre grant opposition .

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.

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