BEFORE CONTROLLER OF PATENTS
THE PATENT OFFICE, DELHI

THE PATENTS ACT 1970
(Section 15)

In the matter of application No. 2488/DELNP/2004 filed on 26th August 2004
deposited by M/S Astrazeneca AB, Sweden

Hearing held on 15th October 2008

Present:

1. Dr. Deepa K. Tiku  ------- Agent representing the applicant
2. Dr. Rohit Rathore  ------- Examiner of Patents & Designs

ORDER

1. M/S Astrazeneca AB, a Swedish company of S-151 85 Sodertiilje, Sweden
through their patent attorneys M/S Remfry & Sagar filed a patent
application No.2488/DELNP/2004 on 26th August 2004 for their invention
related to "Novel Crystalline Forms of the Anti-Cancer Compound Zd1839"
with claim-1 reading as:
"A crystalline form of the compound of the Formula I substantially in the form
of Form 3 ZDI839 DMSO solvate."

2. On the receipt of request for examination on 28th December 2005, this
application was examined and First Examination Report (FER) thereof was
issued on 8th August 2007 vide this office letter No. 2488/DELNP/2004/3864. The examination report inter-alia contained the
objections relating to lack of inventive step u/s 2(1)(j) of the Patents Act 1970
in view of patent document WO9633980, claims falling within the provisions
of clause (d) & (e) of Section 3 of Patents Act 1970 as amended in 2005
alongwith other objections.

3. The agents for the applicant responded to the objections contained in First
Examination Report on 10th December 2007 and resubmitted the documents with amended claims. Revised claim-1 reads:

“A crystalline form of the compound of the Formula I having at least 80% of the compound of the Formula I in the form of Form 3 ZD1839 DMSO solvate and wherein the degree of crystallinity is greater than 80%.”

The applicants have resisted that the subject matter of claims fall within the prohibition of Section 3(d) and submitted that the subject matter of Claims 1 to 9, namely Form 3 ZDI 839 DM80 solvate is patentable as it is a useful chemical intermediate as the inclusion of the steps of DMSO solvate preparation, purification thereof and conversion back to the compound of Formula I is beneficial in terms of yield and purity of the compound of Formula I that may be prepared.

The claimed crystalline form is unusual in that it is easily isolated and is also very stable. The solvate compound may readily be prepared on a commercial scale at a high level of purity and in high yield. In addition, this solvate may readily be converted into the compound of Formula I, in particular into the compound of Formula I in the form of Form I ZD1839 polymorph. This crystalline material does not naturally fall within the group of forms of a known substance, as listed in the explanatory notes relating to interpretation of the Section 3(d), that this aspect of the Patent Law seeks to exclude from patentability. It is not a salt, ester or polymorphic form. It could be described at best as a 'complex' but the applicants consider it would be a travesty of justice if such a formalistic analysis were to be used to deny its patentability.

The key difference is that Form 3 ZD1839 DM50 solvate is useful in improving the manufacturing process for ZD1839. This is not an invention that has the aim of 'ever-greening' the original invention relating to ZD1839. In these circumstances, the applicant submitted that there should be no need to demonstrate that Form 3 ZD1839 DMSO solvate possesses surprisingly beneficial pharmacological efficacy compared to that of the
parent compound, namely ZD 1839. This solvate does possess beneficial physiochemical properties compared to those of ZD1839 as it is easily isolated and is also very stable. It may readily be prepared on a commercial scale at a high level of purity and in high yield. In addition, it may readily be converted into pure ZD1839. Further, Form 3 ZO1839DM80 solvate has physiochemical properties that differ from those of each of ZD 839 and DM50.

As regards objection under Section 3(e), they submitted that since the claimed solvate is novel and inventive compositions prepared using the same may contain a varying range of amount of the said compound. The scope of protection, therefore extend to any amount of the compound being present in a composition prepared using the said solvate. Accordingly, synergism is not required to be established.

As regards WO 98/33980, the applicants submitted that code number ZD1839 was disclosed in International Application WO 96/33980 which has a publication date prior to the priority date of the present Application. The relevant quinazoline compound is disclosed in Example I thereof. However, there is nothing in that would lead the man skilled in the art to contemplate that a crystalline solvate might be useful in the preparation of samples of the compound of improved purity. In particular, there is no indication whatsoever that a DMSO solvate could be prepared, that it would be crystalline, easily isolated and also very stable; nor that it may readily be prepared on a commercial scale at a high level of purity and in high yield; nor that it may readily be converted into pure ZD1839.

3. The revised claims were examined and the objections including claims falling u/s 3(d) of the Indian Patents Act were maintained and accordingly further examination report was issued to the applicant on 4th August 2008. The agent for the applicant responded to the objections on 6th August 2008 by filing a submission as filed earlier alongwith further information that Example 1 on page 37, at lines 1 to 15, provides instruction and data relating to the manufacture of the solvate of Form 3. Instructions are provided in Example 1 concerning the preparation on a substantial 200 kg scale of a complex of the compound known by the code number ZD·1839 with the organic solvent dimethyl sulphoxide (the conventional abbreviation of which is DMSO). Details of quantities of reactants, solvents and reaction temperatures are provided. Details are provided of the conditions required to cause the precipitation of the crystalline complex, namely 'Form 3 ZD1839
DMSO solvate’. Reference is made to the characterisation of the complex by XRPD and DSC analysis. The relevant XRPD and DSC analytical data are provided by way of the data in Figures 7 and 8, the results of which are referred to in the specification on page 10, at line 27, to page 11, at line 3. In addition, a DRIFT spectrum is shown by way of the data in Figure 9, the results of which are referred to in the specification on page 11, at lines 4 and 5. Facts concerning the procedure to be used to convert the DMSO complex to unsolvated ZD1839 are disclosed in Example 3 on page 37, line 29, to page 38, line 4. Details of quantities of materials, solvents and reaction temperatures are provided. Purified ZDI839 on a substantial 161 kg scale is described. It was reiterated that the patent claims concern ‘Form 3 ZD1839 DMSO solvate’ as a chemical compound. The application does not claim any pharmaceutical composition containing the complex. The crystalline complex is not a form of a known substance’ such as a salt, ester or polymorphic form that is intended for administration to a patient. 'Form 3 ZD1839 DMSO solvate', is a useful chemical intermediate. It is not administered to patients. Therefore its medical efficacy or inefficacy is irrelevant to its usefulness as a chemical intermediate.

4. The revised claims and submission filed by the agent were examined but still the objection regarding claims 1-10 falling under section 3(d) of the Patents Act, 1970 maintained. The agent for the applicant requested for an opportunity of being heard in the matter and subsequently a hearing letter along with objections sustained issued on 13th August 2008.

5. The agent in their argument during hearing on 21st November 2008 once again reiterated that the claims does not fall under the purview of Section 3(d). The applicant further submitted that as stated in the patent application on page 1, at lines 3 to 6:-

"The present invention relates to particular crystalline forms of a pharmaceutical compound, to processes for their preparation, to their use in the purification of that pharmaceutical compound, to pharmaceutical compositions comprising them and to their use in therapy.

The relevant pharmaceutical compound is Iressa (registered trade mark), known also as gefitinib and by way of the code number ZD 1839, the structural formula of which is shown as the Formula I of the patent application on page 1, between lines 13 and 15.

As stated in the patent application on page 2, at lines 6 and 7:-
“have now found that certain forms of the compound of Formula I eluding certain solvates thereof are crystalline materials that possess advantageous properties.”

As stated in the patent application on page 3, within the text spanning lines 7 to 15 :-

"A study of the properties of the compound of the Formula I has been performed to discover whether polymorphism and/ or solvate formation is possible. A wide range of recrystallisation solvents of various polarities 'was investigated. From most of these solvents, only a single non-solvated, crystalline form of the compound of the Formula I was obtained which is designated hereinafter as Form 1 ZD 1839 polymorph. Two solvates were also identified as of interest. The first solvate occurred in the presence of methanol and this is designated hereinafter as Form 2 ZD1839 MeOH solvate and the second solvate occurred with dimethyl sulphoxide and this is designated hereinafter as Form 3 ZD 1839 DMSO solvate. We have also found a trihydrate, designated hereinafter as Form 5 ZD 1839 trihydrate-.

It was submitted that, If the planned and actual use of any of the Crystalline forms of ZD1839 that are disclosed in the patent specification Is not therapeutic, the exclusions of Section 3(d) should be deemed not to be relevant. The patent claims are restricted to Form 3 ZD1839 DMSO solvate. As the name suggests, this 'Form 3' is a solvate of the known substance ZD1839. However, regulatory approval for the therapeutic use of Form 3 ZD1839 DMSO solvate has not been and will not be sought by the patent applicant in any country in the World. Rather, Form 3 ZD1839DMSO solvate is being used in a non-therapeutic manner. Form 3 ZD1839 DMSO solvate has proved to be a surprisingly valuable last stage intermediate that is used in the manufacturing process for Iressa (gefitinib; ZDI839). Given its commercial use in a manufacturing process, Form 3 ZD1839 DMSO solvate is clearly not a 'frivolous' version of ZD1839. In addition, there is no question of Form 3 ZD1839 DMSO solvate being used as a therapeutic product to act as an ever-greening version of Iressa (gefitinib; ZDI839). Rather, the invention of Form 3 ZD1839 DMSO solvate is a sequential development, that is, an incremental innovation that builds on the original invention of the product ZD1839. Hence, it is submitted that it is the actual (or intended) use of the compound that is the subject of the patent claims that should govern the applicability of Section 3(d).

It was further submitted, that Form 3 ZD1839 DMSO solvate is a useful chemical intermediate. This is fully supported by the description and in this regard, we submit as follows:
"In particular, it has now been found that Form 3 ZD1839 DMSO solvate is crystalline and that, surprisingly, that form has advantageous properties. Further, we have discovered that Form 3 ZD1839 DMSO solvate is unusual in that it possesses a crystalline physical form that is easily isolated and is also very stable. Moreover, this solvate may readily be prepared on a commercial scale at a high level of purity and in high yield. In addition this solvate may readily be converted into the compound of Formula -1, in particular into the compound of Formula I the form of Form1 ZD1839 polymorph. Overall, the inclusion of the steps of DMSO solvate preparation, purification thereof and conversion back to the compound of Formula I is beneficial in terms of yield and purity of the compound of Formula 1".

The agent further submitted that the statement therein that “steps of DMSO solvate preparation, purification thereof and conversion back to the compound of Formula I is beneficial in terms of yield and purity of the compound of Formula I", whilst not making specific use of the word 'intermediate', is a clear disclosure that Form 3 ZD1839· DMSO solvate is a chemical intermediate that is useful in the manufacture of Iressa (gefitinib; ZD1839) on a commercial scale. The processes for preparing Form 3 DMSO solvate and its conversion to the compound of Formula I are disclosed in the patent specification from page 18, line 25, to page 21, line 26. For example, the process for preparing Form 3 DM50 solvate is disclosed in the patent specification from page 18, line 25, to page 19, line 3, where it is stated that: ‘We have discovered a process for preparing a crystalline form of the compound of the Formula I substantially in the form of Form 3 ZD1839 DMSO solvate, preferably substantially free of any other ZD1839 solvate or any Form 1 ZD1839 polymorph. Such a process provides a further aspect of the present invention and comprises, for example, the steps of:

- heating a mixture of the compound 4-3' -chloro-4'-fluoroanilino)- 7-methoxy-6-(3-morpholinopropoxy)quinazoline in dimethyl sulphoxide or a solvent mixture containing dimethyl sulphoxide and a co-solvent until dissolution has occurred, maintaining the mixture at a temperature below that at which nucleation has commenced; and

The process for the conversion of Form 3 DMSO solvate to the compound of Formula I is disclosed in the patent specification on page 20, at lines 21 to 30, where we state that:

In addition Form 3 ZD1839 DMSO solvate may readily be converted into the compound of Formula 1, particularly into Form I ZD1839 polymorph. Overall, the inclusion of the steps of DMSO solvate preparation, purification thereof and conversion into Form 1 ZD1839 polymorph is beneficial in terms of the yield and purity of the Form 1 ZD1839 polymorph so obtained. Such a
process for the preparation of the compound of Formula I substantially in the form of Form 1ZD1839 polymorph provides a further aspect of the present invention and comprises, for example, the steps of:
(a) washing Form 3 ZD1839 DMSO solvate with a solvent or solvent mixture substantially to remove dimethyl sulphoxide.

With regard to the data in Examples 1 (on page 37) and Example 3 (on pages 37 and 38), the Examiner, seeking to evaluate the Section 3(d) requirement for an enhancement of the known efficacy of the known substance Iressa (gefitinib; ZD1839) considered that the information did not sufficiently prove the enhanced efficacy (improvement/usefulness) of Form 3 ZD1839 DMSO solvate. In view of the above applicant stated that Section 3(d) is not properly applicable to the factual situation of an incremental innovation relating to a non-therapeutic chemical intermediate due to disclosure made in example 1 as given below:

"Example 1 Form 3 ZD1839 DM SO solvate
4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline monosolvate with dimethyl sulphoxide With warming to about 75°C, 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (204 kg) was dissolved in a mixture of ethyl acetate (1021 litres) and dimethyl sulphoxide (181 litres) containing diatomaceous earth filter aid (5 kg). The resultant mixture was filtered and ethyl acetate (78 litres) was used to wash the filter aid solid. The filtrate and washings were combined and cooled initially to about 10°C. The mixture was then heated to about 40°C for 1 hour. The warm mixture was cooled to O°C at a rate of about 10°C per hour. The resultant solid was collected by filtration. There was thus obtained Form 3 ZD1839 DMSO solvate as shown by XRPD and DSC analysis. The 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline used as a starting material is disclosed in International Patent Application WO 96/33980 within Examples I and 10. The material may also be obtained as described in Example 4 hereinafter".

Thus, instructions are provided in that Example 1 concerning the preparation on a substantial 200 kg scale of a solvate of the compound known by the code number ZD1839 with the organic solvent dimethyl sulphoxide (DMSO). Details of quantities of reactants, solvents and reaction temperatures are provided. Details are provided of the conditions required to cause the precipitation of the crystalline complex, namely 'Form 3 ZD1839 DMSO solvate'. This information supports the statements on page 3, at lines 18 to 21, that this solvate is easily isolated and is also very stable and that it may readily be prepared on a commercial scale at a high level of purity and
in high yield. Reference is made in Example 1 to the characterisation of the complex by X-ray powder diffraction (XRPD) data and differential scanning calorimetry (DSC) analysis. The relevant XRPD and DSC analytical data are provided in the patent specification by way of the data in Figures 7 and 8, the results of which are referred to in the patent specification on page 10, at line 27, to page 11, at line 3. In addition, a diffuse reflectance infrared fourier transform (DRIFT) spectrum is shown by way of the data in Figure 9, the results of which are referred to in the specification on page 11, at lines 4 and 5.

Hence, the existence of this new solvate is not merely a statement of the Patent Applicant that is unsubstantiated by any data. The data do not relate to enhancement of the known efficacy, the therapeutic efficacy, of Iressa (gefitinib; ZD1839) as the solvate is not used (and will not be used) as a therapeutic agent. Instead, the data relate to the formation of this new solvate, namely ‘Form 3 ZD1 839 DMSO solvate’, and its use within a manufacturing process involving ZD1839. This process is used on a commercial scale as it is beneficial in terms of the yield and purity of the ZD1839 that is obtained. With regard to the conversion back to unsolvated ZD1839, it is stated in the patent application on page 37, line 29, to page 38, line 4, that: "Example 3 Process of conversion of Form. 3 ZD1839 DMSO solvate to Form. 1 ZD1839 polymorph. Form 3 ZD1839 DMSO solvate (from Example 1) was washed with ethyl acetate (58J litres). The washed solid was mixed with ethyl acetate (895 litres) and the resultant slurry was stirred and heated to 34°C for about 1 hour. The mixture was then cooled to Cand held at that temperature for 2 hours to allow the conversion to proceed. The resultant solid was separated by filtration, washed with ethyl acetate (580 litres) and dried in a flow of warm nitrogen gas (60°C). There was thus obtained Form 1 ZD1839 polymorph (161 kg) as shown by XRPD and DSC analysis".

Thus, details of quantities of materials, solvents and reaction temperatures are provided and purified ZD1839 on a substantial 161 kg scale is described. Thus, in particular, it is acknowledged that it is stated therein that Form 3 ZD1839DMSO solvate is a therapeutically active entity. However, assessment of this solvate’s therapeutic activity has not progressed to (and will not progress to) the evaluation of any of the pre-clinical studies (for example, of pharmacokinetic properties), laboratory animal studies (for example, of pharmacological efficacy and toxicity) or any of the clinical trial studies that would be required to be submitted for review by the appropriate regulatory authorities before an appropriate pharmaceutically-acceptable formulation containing that solvate could be approved for dosing to patients.
It was further submitted that it should make no difference whether the new intermediate was the first intermediate in the multi-step process, a middle intermediate in the multi-step process or the last intermediate in the multi-step process. The new compound being claimed would be a chemical intermediate. It would not be a drug or a pro-drug. There would not be a granted patent claim to a pharmaceutical composition containing the intermediate as there would be solvent and its DMSO solvate form can be prepared, crystallized from the solvent solution and isolated. The pure solid DMSO solvate can then be washed with an organic solvent to convert the DMSO solvate back to a purified form of ZD1839. The resultant purified ZD1839 can then be dosed to patients. The DMSO solvate is not dosed to patients. With regard to the present Application, the patent claims considered by the Examiner do not contain a pharmaceutical composition claim comprising the DM50solvate. It is simply a useful chemical intermediate. It is submitted that it is fundamentally wrong to consider the DMSO solvate to be an 'ever-greening' version of the drug ZD1839. It is submitted that it is fundamentally wrong to apply the requirements of Section 3(d) and request that data have to be presented to show that this chemical intermediate has enhanced pharmaceutical properties compared to the drug. Thus, in the present case, the comparison does not involve pharmacological efficacy as the Form 3 ZD1839 DMSOsolvate is not used (or intended to be used) as a drug. Rather, it is submitted that the properties of Form 3 ZD1839 DMSO solvate that are relevant to its actual use are its physiochemical properties. Form 3 ZD1839 DMSO solvate has the property of being a chemical intermediate used in the manufacture of the known substance Iressa (gefitinib; ZD1839). Form 3 ZD1839 DMSO solvate has the surprising property of being crystalline and of being readily isolable. Its properties are advantageous as it is easily isolated and is also very stable such that it may readily be prepared on a commercial scale at a high level of purity and in high yield. This is an important, practical process improvement such that it is commercially worthwhile to add the additional steps of DMSO solvate preparation, isolation and conversion to ZD1839 rather than trying to isolate sufficiently pure ZD1839 directly. Even with inclusion of these extra steps, the yield of pure ZD1839 that is isolable increases from about 70% to about 80% and the amount of one of the by-products that is normally seen is reduced significantly.

6. I have examined all the submissions and revised claims given by the agent. It is observed that the present invention relates to crystalline solvate of already known compound Form 3 ZD1839 in the prior art. The applicant
Submission that claimed compound is simply a useful chemical intermediate and advantageous as it is easily isolated and is also very stable such that it may readily be prepared on a commercial scale at a high level of purity and in high yield and such property has practical process improvement such that it is commercially worthwhile to add the additional steps of DMSO solvate preparation, isolation and conversion to ZD1839 rather than trying to isolate sufficiently pure ZD1839 directly does not establish the efficacy for the claimed crystalline form of known compound. It may be noted that under the provisions of section 3(d) mere discovery of a new form of known substance which does not result in the enhancement of known efficacy of that substance is not patentable. The explanation to this provision further specified that for the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance unless they differ significantly in properties with regard to efficacy. It may be recalled that in Novartis case the honourable High Court of Chennai has held that in order to prove the efficacy it requires pharmaceutical efficacy. Therefore the claimed new form 3 ZD1839 DMSO solvate of compound ZD1839 is not patentable u/s 3(d) of the Patent Act, 1970. However if the applicants are interested claim 11 may be considered for grant of patent on meeting the requirements under the law provided they delete claim 1-10 and submit the revised claim and description within one month from the date of issue of this order.

Having considered all the facts, submission made by the agent for the applicant during the hearing and as well as all the documents on record and also in view of my above findings, I hereby refuse the claims 1-10 to proceed further for grant of patent since they are not patentable under section 3(d) in accordance with the provisions of the Patents Act 1970 with the direction that claim 11 may be allowed to proceed for grant if the applicants so desires to comply with the directions as mentioned above..

Dated, the 12th day of August, 2009.

(Dr. K.S. Kardam)
Deputy Controller of Patents & Designs

Copy to: M/S Remfry & Sagar,
Gurgaon, Haryana, India