PRE-GRANT REPRESENTATION BY WAY OF OPPOSITION
UNDER SECTION 25(1) OF THE PATENTS ACT
1970(39 OF 1970) AND RULE 55 (1) OF THE RULES
AS AMENDED BY THE PATENTS (AMENDMENT) ACT, 2005

The Patent Controller,
Chennai.

Re: Patent Application No. 1602/MAS/98 filed on 17 July 1998 titled "Crystal Modification of N-Phenyl-2-pyrimidineamine derivative, processes for its manufacture and its use"

STATEMENT OF FACTS / EVIDENCE

1. Cancer Patients Aid Association (CPAA), a charitable organization registered under the Societies Registration Act, 1860 in January 1970 and under the Bombay Public Trusts Act, 1940 in February 1970, having its main office and place of business at Mumbai, hereby makes a representation by way of opposition against the grant of patent application, titled: "Crystal Modification of N-Phenyl-2-pyrimidineamine derivative, processes for its manufacture and its use", made by Applicant Novartis AG of Schwarzwaldallee 215, 4058 Basel, Switzerland, bearing Indian patent application No.1602/MAS/98 filed on 17 July 1998.

2. The patent application was filed by Novartis AG at the Patent Office in Chennai, therefore, the Patent Controller has the jurisdiction to hear this pre-grant opposition in Chennai. We would like to be heard as per provisions under rule 55(1) of Patent Rules, 2005.

3. We have strong and valid grounds for opposing the grant of the patent and are consequently filing this written pre-grant representation/ opposition to the patent application as referred to above, against the grant of patent on claims 1 to 12 and 14 to 16 of the grounds of the patent application as pre-grant opposition under Section 25(1) of the Patent Act 1970 (amended up to date by the Patents (Amendment) Act, 2005), hereinafter known as "the Act.

4. Section 25 (1): Opposition to the patent where application has been published but not granted. The following grounds and evidence sets out the basis of the opposition to the application:-

PRE-GRANT OPPOSITION ON THE FOLLOWING GROUNDS:-

a. Prior publication and prior knowledge:

1. Under Section 25 (1)(b)(i) and (ii) the application should not be granted on the ground that the invention so claimed in any claim of the complete specification has been published before the priority date of the claim in any specification filed in pursuance of an application for a patent made in India on or after 1 January 1912 or elsewhere, in any other document. Furthermore, under Section 25(1)(d) the application should not be granted on the ground that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of the claim.
2. The purported invention of methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N[4-methyl-3-(4-pyrindin-3-yl)pyrimidin-2-ylamino)phenyl] benzamide, comprising certain crystals, especially the β-crystalline form is not a new product and that it has been published previously.
3. It is claimed by the Applicant for the patent – Novartis, that the preparation was published on 6 October 1993 in numerous countries, however, the compound is exemplified in the publications only in the free form, not as a salt.
4. We submit that the purported invention so far as claimed in the complete specification has been published before the priority date of the claim in a specification, that is before 17 July 1998.
5. The Patent Applicants had filed a patent claim for the same substance in the United States (U.S.) on 28.4.1994 viz. for "pyrimidine derivatives and processes and preparation thereof". The US authorities granted the patent to the Patent Applicant on 28.5.1996 thereof, which disclosed the Mesylate salt of Imatinib. (American Patent No. 5521184, filed April 28, 1994, priority date April 3, 1992 publication date May 28, 1996)
6. The priority for the U.S. patent application was claimed on the basis of the Switzerland patent Application filed on 3.4.1992 viz. 1083 of 92.
7. A patent claim for the same article was also filed in Canada on 1.4.1993 basing itself on the priority of Swiss application, which was granted by the Canadian authorities on 26.11.2002 (Patent No. 2093203, filed April 1st 1993, priority date April 3 1992, publication date Nov 26, 2002).
8. It is submitted that on a reading of the specifications for which the patent was granted in Canada and subsequently in the USA, it is clear that the patent was granted not only for the compound in its free state, but also for all its salts.

9. Claim 29 of the Canadian Patent states: 'N-(S(4(4- methlpipenazino-methyl)- benzoylamido)- 2- methyl-phenyl)- 4-(3-pyridyl)- 2- pyrimidine-amine or a pharmaceutically acceptable salt thereof according to claim.'
10. Further, the US Complete specification states, (US Patent No. 5521184 pg. 9) 'Owing to the close relationship between the novel compounds in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification of the novel compounds or for the identification thereof, hereinbefore and hereinafter any reference to the free compounds should be understood as including the corresponding salts, where appropriate and expedient.'
11. It is therefore amply clear from the above, that the specification for the patent that was given in Canada and in the U.S. 1993 and in 1994, respectively, was not only for the compound (in the free form) mentioned above, but also for all its salts and the same was published prior to 17 July 1998.
12. It is therefore amply clear that the salt form of 4-(4-methylpiperazin-1-ylmethyl) N-[4 - methyl-3-(4-pyridin-3-yl)pyrimidin- 2- ylamino)phenyl benzamide has already been published in Canada and the USA well before the priority date of the Indian Application, and was publicly known in India before the priority date that is since 1993.
13. Therefore, it is submitted that the application should be refused and rejected on the ground of prior publication and prior knowledge under Section 25(1)(b) and 25(1)(d) of the Act.

b. Does not involve an inventive step

1. The present invention is obvious and does not involve an inventive step as defined under Section 2(ja) of the Act, and disentitles it from being granted a patent under Section 25(e) on the ground that the invention so far as claimed in the claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in Section 25(1)(b) of the Act or having regard to what was used in India before the priority date of the applicant's claim .
2. The complete specification of the Indian patent application indicates the process in which the beta-crystal form is obtainable.
3. The steps as stated in the patent application is that by merely processing the substance in the alpha form with alcohol in the presence of some water or mixtures at a particular temperature and then initiating crystallisation by adding the beta form as the seed.
4. It is submitted that there is no inventive step in getting the beta form of the substance and that it is a procedure obvious to the person skilled in the field and known in the field of science for years. The process involves no

inventive step of any sort and does not satisfy the criteria of non-obviousness.

5. The process does not show any technical advance as compared to the existing knowledge. In fact, no where in the patent application is it stated how the process of getting the beta crystalline form of Imatinib Meyslate is an inventive step or that it is not obvious to a person skilled in the art.
6. Further, there is no economic significance as it is not a new invention. Economic significance must be read in conjunction with the requirement of non-obviousness. The applicant has not shown any facts that show that the alleged invention is economically significant. The fact that it has a value does not mean that there is economic significance to it.
7. It is submitted that it does not require an inventive step to produce it. Therefore, the patent cannot be granted in the above mentioned application for patent as it is disentitled under section 25(1)(e) of the Act.

c. Not an invention

1. Under section 25 (1)(f) the subject of the claim is not an invention within the meaning of Section 2(j) of the Act, or is not patentable under the Act, the patent application should be rejected. It is not a new product or process involving an inventive step.
2. The salts of Imatinib Meyslate as polymorph exists naturally in two forms, namely, α - alpha and β- beta forms. The β-crystalline form of Imatinib Meyslate is naturally existing and the therefore not an invention. The beta form is naturally the preferred form generated when the base is converted to the meyslate salt. The beta form is generated automatically in the natural form. There is no invention required.
3. Deriving a salt from free acid is the most commonly known step ever since the field of chemistry came to be practiced. The alpha and beta forms are merely different crystal forms in the solid state. The structures of both the forms are the same, with the beta form being different only a light refraction of the alpha form.
4. In any event, the crystalline form of Imatinib Meyslate was disclosed in the pre 1995 Patent Applications in other countries. It was not identified as alpha crystalline form. However, the Indian patent Application describes a form called the beta crystalline and further falsely and wrongly claims that the earlier form was the alpha crystalline.
5. It maybe noted that once the alpha form is available, the beta form can be obtained automatically. It is therefore not an invention and cannot be considered to be a new product.
6. Therefore, on this ground too, under section 25(1)(f) of the Act, the patent cannot be granted.

d. Insufficient description

1. The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed, and therefore should be rejected under section 25(1)(g).
2. The patent application has failed to disclose the valid and relevant material regarding the alleged invention.
3. We respectfully submit that the alleged invention claims with respect to the purity of beta-crystalline form vis-à-vis the alpha-crystalline form is not sustainable. We quote: 'The term "essentially pure" is understood in the context of the present invention to mean especially that at least 90, preferably at least 95, and most preferably at least 99 per cent by weight of the crystals of an acid addition salt of formula 1 are present in the crystal form according to the invention, especially the beta-crystal form'.
4. The Applicants have themselves admitted that their invention is "essentially pure" which as per the applicant's own claim is 90-99% pure. The applicant has not produced any evidence available to prove that the product which is the subject matter of alleged invention, namely the beta-crystalline form does not contain the product which is the subject matter of the patent application prior to 1995 (US Patent No. 5521184 with a priority date of as early of 1993) and which is in the public domain.
5. The process for the preparation of beta-crystalline form has alpha- crystalline form as the starting material. The applicant has failed to show the form of the final product.
6. In the applicant's own words beta-crystalline form has greater stability and is thermodynamically stable at room temperature, while alpha- crystalline form is not thermodynamically stable at room temperature. It maybe noted that the alpha form is also metastable as the beta form. The alpha form by itself may not be as stable to humidity as the beta form for long term storage. But one versed in the art can easily formulate with other acceptable excipients and make a good tablet or capsule with sufficient stability for storage. Therefore, even a superiority claim of the beta form over the alpha form is untenable for a patent.
7. It may be noted that the beta form is more stable under humidity conditions and therefore will help storage and transport. However, the Applicant has not shown that the original mixture reported in the earlier patent is not storable or stable. Further, mere stability to humidity cannot be a sufficient ground for an inventive step. Solvent for crystallization and different crystal forms solidifying from different solvents is generic and no inventive contribution can be claimed for that.

8. The applicant has failed to show that the alpha- crystalline form, which is allegedly less stable at room temperature does not itself transform into beta-crystalline form automatically. In which case, the subject matter of present application becomes prior disclosure, prior patent and prior art in view of the pre-1995 application and subject matter thereof. The industrial applicability of the present invention over the above disclosed invention is too narrow and too insignificant as admitted or not proved by their specification and claims thereof.

e. Patent Application not made within one year from the date of filing in a convention country.

1. The application was not filed within twelve months of the date of the first application for protection for the invention made in a convention country by the applicant and as a result should be refused under section 25(1)(i) of the Act.
2. It is pertinent to note that it appears that on 17.7.1998 a convention application for patent in India was made under section 135 of the Act. It appears that a priority date claimed in the patent application was on the basis of the application for patent made in Switzerland on 18.7.1997. However, Switzerland was notified as a convention country only on 30.11.1998 by way of a notification in the official gazette in India. Therefore, (i) on 17.7.1998, when the application was made in India, Switzerland was not a notified country in India; (ii) the patent application filed therefore should not and could not have been a convention application, but an application that should be accompanied by a provisional or complete specification as envisaged under section 7 (4) of the Act; (iii) the novelty, if any, of the patent application itself was lost.
3. In any event, the complete specification does not state the novelty in the purported invention.
4. Therefore, the application for patent deserves to be rejected under section 25(1)(i) of the Act.

f. No difference in efficacy

1. It may be noted that under the Patents (Amendment) Act, 2005, under section 3 (d) it has been clearly stated that a mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance is not patentable. In the explanation of that section too it is stated that salts, combinations and other derivatives of

known substance shall be considered the same substance, unless they differ significantly in properties with regard to efficacy shall not be patentable.

2. The compound or molecular structure of the material or the drug is the same and is not different in the beta crystalline form. It is only a different physical form of the same compound. Patent Law in India does not recognise esters and salts as new entities and therefore different crystal forms cannot be considered as new entities and the claim of the Applicant should be rejected.
3. As stated above, the beta form is obvious and cannot be considered an invention.
4. Further, the β-crystalline form of the salt can be patented only if it differs significantly in properties with regard to efficacy from the alpha-form. The complete specification of the Indian application states at various places, that the properties of the β-form are the same as that of the free base. Further, the Applicant has not shown in the application the differences in pharmacokinetics or efficacy. Bio-availability and efficacy are not proportional and the Applicant has not differentiated the two polymorphs (crystal forms) on the basis of efficacy. Both the beta and the alpha forms will bind to the SCF receptor.
5. The specification itself states, as seen above, that all the indicated inhibitory and pharmacological effects are also found with the free base or other salts thereof. The only alleged difference in the beta-crystal form of the methanesulfonic acid addition salt of a compound of formula I is its use 'in the treatment of one of the said diseases or in the preparation of a pharmacological agent for the treatment thereof'. There is, however, no mention, whatsoever, of what the said disease is that is said to be treated, or any difference in properties that enhances efficacy which might entitle it to a patent.
6. In India and other countries new drugs must be approved by the Food and Drug Administration (FDA) through several phases of clinical trials before they are manufactured, advertised and sold. In the U.S., new drugs and medical devices must be approved by the US FDA before they can be advertised or sold to the general public. This approval requires the drugs and medical devices to go through several *phases* of clinical trials. According to the Clinical Trials Database and FDA standards, efficacy is, "the maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective as the dose tested and against the illness for which it is prescribed. In the procedure mandated by the Food and Drug Administration, phase II clinical trials gauge efficacy, phase III trials confirm it."
7. It is only on the performance of such prescribed tests can efficacy be estimated and thereafter compared to that of the α–form. Only after these prescribed tests show a significant difference in properties with regard to

efficacy can the beta crystal form be independently patented. There have been no such tests done to estimate the efficacy of the beta-crystalline form as compared to the α–form. It is only when the prescribed tests have been conducted and evaluated by an independent agency, that measures the efficacy of the beta-crystalline form in comparison with Formula I, and a significant difference been proved, can such a new salt-form (the beta form) of a known compound be given a patent.

8. It may also be noted that the drug *Gleevec* containing the compound Imatinib Mesylate in the beta crystalline form was treated as an "orphan drug" in the US, which means that the FDA in the USA gave permission without doing stringent clinical trials, which is normally done with other pharma products. The trials and the FDA approval to treat the drug as an orphan drug were only for its treatment of chronic myeloid leukemia (CML) and for no other disease.
9. However, the applicants for the patent have made claims for diseases such as tumor diseases, small cell lung cancer, non-malignant proliferative disorders such as atherosclerosis, thrombosis, psoriasis, scleroderma and fibrosis as well as protection of stem cells, for example to combat the haemotoxic effect of chemotherapeutic agents, such as 5-fluoruracil and in asthma. They claim that it may especially be used for the treatment of diseases which respond to an inhibition of the PDGF receptor kinase. They claim that it also prevents the development of multi-drug resistance in cancer therapy and may be used to advantage in combination with other anti tumor agents.
10. The applicants have not shown any where how the drug for which they seek a patent is more efficacious than any other prior drug for any of the above mentioned diseases. There are no clinical trials studies to show that the drug is more efficacious in any of the diseases mentioned herein above. It may be noted here that the Applicant has to show the clinical trials done on all the diseases and not just CML for which the drug is treated as an orphan drug. For all other diseases the stringent clinical trials would have to be shown and efficacy would have to be established clearly and without doubt.
11. It is submitted that in the absence of the efficaciousness of the claim, the patent cannot be granted.
12. The beta crystalline form of the salt, as may be seen from the complete specification, is not therapeutically different and does not in any way differ with regard to efficacy from the alpha-crystalline form disclosed prior to the priority date of this patent.
13. The complete specification of the Indian Application only mentions the differences in chemical properties which have absolutely no impact on the therapeutic or pharmaceutical properties of the compound, and are merely minor modifications of the already known compound. While, the applicant

claims in the Complete Specification that the beta- crystalline form is better than the alpha- crystalline form for manufacturing the pharmaceutical preparation, it has in no way substantiated this claim. As can be seen, the therapeutic and pharmaceutical uses of the beta-form that are given are identical to that of the alpha form. Merely giving the difference in chemical properties between the two with no difference in efficacy does not entitle them to a patent.

g. Commercial exploitation of the invention that causes serious prejudice to human health:

1. By granting a patent for the alleged invention, it would only allow for commercial exploitation of the purported invention, thereby excluding all others, causing serious prejudice to human health.
2. It is submitted that cancer is a disease that is life threatening and a person affected requires monitoring and treatment life long. However, the treatment is not affordable in India and people affected by cancer die due to non-affordability of treatment.
3. The proposed patent application not only deserves to be rejected on the grounds stated herein above, but also should be rejected as the applicants have only used the purported invention for commercial exploitation, by selling the drug in the Indian market at Rs.1,20,000/- per month, which cannot be afforded by patients affected by chronic myeloid leukemia.
4. Such monopolizing of the drug at the above-mentioned exorbitant price is, thereby causing an adverse affect on and serious prejudice to public health. It may be noted that this in itself is contrary to public order and morality, and the patent should not be granted.
5. It is therefore submitted that this purported invention cannot be considered an invention under Section 3(b) of the Act, and therefore should not be granted a patent.

h. Mere admixture is not an invention

1. Under Section 3(e) ‘a substance obtained by a mere admixture resulting only in the aggregation of the properties of the compound thereof or a process for producing such substance’, is not an invention under this Act.
2. It is humbly submitted that said compound is a known compound and a simple obvious and known process has produced the beta crystalline form of the compound. The substance obtained is a mere admixture of the compound itself and is therefore not patentable.

5. We hereby request you to reject and refuse the above patent application on grounds of:-

   (1) Prior publication and prior knowledge under Section 25(1)(b) and 25(1)(d) of the Act.
   (2) It is obvious and involves no inventive step as defined under Section 2(ja) of the Act and deserves to be rejected under Section 25(e).
   (3) Not an invention as defined under section 2 (j) and ought to be rejected under section 25(1)(f) of the Act.
   (4) It does not sufficiently and clearly describe the invention or the method by which it is to be performed, and therefore should be rejected under section 25(1)(g).
   (5) Patent application not made within one year of filing in a convention country.
   (6) It not being an invention under sections 3 (b), (d) and (e) i.e. non-patentability due to lack of novelty, it being obvious, it being a mere admixture, it not being more efficacious and is used only for commercial exploitation.

6. We further request you to grant us a hearing as per provisions given under rule 55(1) of Patent (Amendment) Rules, 2005.

   Thanking you,
   Yours truly,

   Mr. Y.K. Sapru
   For Cancer Patients Aid Association

   Encl: 1. Patent Application in the USA
   2. Patent Application in Canada

   Date: 22.9.2005