POST-GRANT OPPOSITION
UNDER SECTION 25(2) OF THE PATENTS ACT, 1970 (39 OF 1970)
AS AMENDED BY THE PATENTS (AMENDMENT) ACT, 2005
READ WITH RULE 55A OF THE PATENT RULES, 2003

To
The Controller of Patents,
The Patent Office
At Mumbai.

Re: Patent No. 195367 granted on 7 June 2005 and published on 3 February 2006 to Application No. IN/PCT/2000/00553/MUM filed on 27 October 2000 by Bristol-Myers Squibb bearing title "Process for preparing form 1 of crystalline EFV"

STATEMENT AND SUPPORTING DOCUMENTS

1. The Delhi Network of Positive People (DNP+), a community-based non-profit organisation, registered under Societies Registration Act, XXI of 1860 bearing registration no. S-52850, having its office at House No. 136, Village Neb Sarai, New Delhi 110 068, hereby files an opposition under section 25(2) of the Patents Act, 1970, as amended by the Patents (Amendment) Act, 2005 (the "Act") against the grant of patent No. 195367 to Application titled "A process for preparing Form 1 of Crystalline Efavirenz" bearing Indian patent application No. IN/PCT/2000/00553/MUM filed on 27 October 2000 (the "Application") by Bristol-Myers Squibb Pharma Company (the "Patentee"). This representation is proper under section 25(2) of the Act as the grant of patent was published on 3 February 2006.

2. DNP+ is a regional network and member of the Indian Network for People Living with HIV/AIDS. The essence of DNP+ is to provide a

voice for persons living with HIV/AIDS (PLHAs) at the local, regional and national levels in order to facilitate systemic change in critical areas such as care and support, access to treatments and addressing issues of discrimination facing PLHAs in Indian society. Of particular concern to the Opponent is the impact of the patent regime on PLHAs' access to safe, effective and affordable HIV/AIDS treatments. The Opponent therefore has a direct interest in the grant of a patent to this Application and is a person interested within the meaning of the Act.

3. The appropriate office for a post-grant opposition as notified in the Patent Official Journal dated 3 February 2006 is the Patent Office at Mumbai, where the Application was filed. The Patent Office at Mumbai has examined and granted a patent to the Application. Therefore, the Patent Office at Mumbai has jurisdiction to hear this post-grant opposition.

4. Relevant law: Though the examination of the application began in 2002, a patent was granted only in June 2005 after the amendment of the Act, which came into retrospective effect from 1 January 2005. Therefore, it is submitted that the provisions of the amended 2005 Act 2005 would apply to the present application.

5. Interest of Opponent: The grant of a patent to drugs or processes for manufacture of drugs inevitably allows the patentee to exclude other pharmaceutical companies from manufacturing the drug or using the protected process for manufacture for a period of twenty years and thereby set high prices for the drugs. The problem of non-affordability of essential drugs is exacerbated by such patent protection. The grant of frivolous patents for alleged inventions, which are obvious to a person skilled in the art, puts drugs out of the reach of millions who require it and also impedes actual scientific advancement.

6. The patent relates to a process for preparing a crystalline form of Efavirenz, a reverse transcriptase inhibitor, a treatment for Human Immuno-deficiency Virus (HIV). It is estimated that there are at least 5.2 million persons living with HIV in India. While at present, there is no cure for HIV, it has become a chronic but manageable lifelong condition for people who can afford treatment, which comprises antiretroviral drugs such as the product obtained by the alleged invention at issue. Due to the inability of PLHAs in the developing world to purchase these medicines, HIV remains a death sentence for them. Efavirenz is part of the first line treatment for PLHAs, when their CD4 count falls below 200. It is included in the ARV rollout programme of the Government of India, under which the government provides free first line treatment to PLHAs. Though available through the government ARV rollout, there was a shortage of Efavirenz last year due to problems of drug procurement. As a result, PLHAs who were on Efavirenz had to purchase it. The Opponent, being a representative organisation of PLHAs, is therefore vitally interested in the outcome of the present proceedings.

7. India, being a signatory to the *Trade Related Aspects of Intellectual Property Rights* ("TRIPS"), was obliged to extend a twenty-year patent protection to pharmaceutical products and processes by 1 January 2005. However, given the implications of TRIPS on affordability and accessibility of medicines, the Doha Ministerial Conference adopted the *Doha Declaration on the TRIPS Agreement and Public Health* (the "Doha Declaration") in 2001. Paragraph 4 of the Doha Declaration, in relevant part, states "we affirm that the [TRIPS] Agreement can and should be interpreted and implemented in a manner supportive of WTO members' right to protect public health

and, in particular, to promote access to medicines for all". (emphasis added).

8. Cognisant of the public health concerns and the Doha Declaration, Parliament introduced certain provisions, while passing the *Patents (Amendment) Act, 2005*, to ensure that trivial claims are not granted patents.

9. Claim 1 of the patent relates to a recrystallisation process for preparation of Form 1 of crystalline Efavirenz, a known compound at the material time. This process comprises crystallising Form 4 of crystalline Efavirenz from a solution of tetrahydrofuran-heptane wherein the solution of tetrahydrofuran-heptane is at a 5% concentration of tetrahydrofuran and is reduced to 1% of tetrahydrofuran and then heating Form 4 thus obtained to a temperature of 80–100 °C. Form 1, as described by the Patentee in the complete specifications, is characterized by X-ray diffraction pattern in accordance with Figure 1, differential scanning calorimeter thermogram in accordance with Figure 6, and has a melting point of 138–140° C.

Background of the alleged invention

10. On 7 August 1992, Merck & Co., Inc. filed a patent application in the United States bearing Ser. No. 926,607 claiming a class of benzoxazinones, including Efavirenz, which could be used as reverse transcriptase inhibitors of HIV transcriptase. On 21 May 1996, Merck & Co. was granted a patent, being US 5519021, for the claimed class of benzoxazinones including Efavirenz. US 5519021 discloses the use of hexane to crystallise Efavirenz.

11. Subsequently, various processes for the synthesis of benzoxazinones were discovered and claimed in patent applications in the United States and corresponding applications under the Patent Cooperation Treaty ("PCT"), which were filed and published before the priority date of the Application. These patent applications disclose the use of toluene and heptane as solvents to crystallise Efavirenz. The Opponent will refer to the relevant documents in due course.

12. The Opponent submits that use of the technique of recrystallisation to purify a compound with liquid solvents has long been known to a person skilled in the art. Arthur I. Vogel in *A Textbook of Practical Organic Chemistry* (Third Edition 1956, New impression 1974, Longman Group Limited London) at pages 122–139, a copy of which is hereto annexed and marked as **"Exhibit A"**, describes that one mode of recrystallisation consists in dissolving the substance to be purified (A) in a solvent (C) at or near the solvent's boiling point where the solubility of the impurity (B) is greater that that of the substance to be purified (A). This results in crystallisation of the substance to be purified (A) leaving the impurities (B) in the mother liquor. Recrystallisation can be carried out using a single solvent or a two-solvent system, i.e. "solvent pairs".

13. The Opponent submits that use of organic solvents to crystallise compounds has been long known in the art. For example, Kathryn Nass in "Rational Solvent Selection for Cooling Crystallizations", Ind. Eng. Chem. Res. 1994, 33, 1580–1584, a copy of which is hereto annexed and marked as **"Exhibit B"**, teaches a solvent selection strategy for choosing crystallisation solvents on the basis of calculation of the maximum theoretical yield of solvents. Solvent candidates studied by Nass include heptane, toluene and tetrahydrofuran.

14. Further, Vicki J. Barwick in "Strategies for solvent selection – a literature review", *Trends in Analytical Chemistry*, vol. 16, no. 6, 1997, a copy of which is hereto annexed and marked as **"Exhibit C"**, reviews existing literature and lists properties of known solvents such as heptane, toluene and tetrahydrofuran. Barwick also describes methods for selecting alternative solvents when an analyst is faced with problems of toxicity and legislation restricting use of certain chemicals.

15. The Opponent further states that on 17 July 1997, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use issued parent guidelines titled "Impurities: Guidelines for Residual Solvents Q3C(R3)", a copy of which is hereto annexed and marked as "**Exhibit D**". These guidelines identify and recommend use of less toxic solvents and describe toxicologically acceptable levels for residual solvents, i.e. "organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products". The document classifies solvents into three classes, viz. Class 1 solvents that should be avoided, class 2 solvents which should be limited in pharmaceutical products and class 3 solvents that are regarded as less toxic and of lower risk to human health. As of 1997, toluene and hexane were classified as Class 2 solvents, while tetrahydrofuran and heptane were classified as Class 3 solvents. Therefore, tetrahydrofuran was a known solvent that was considered to be safer than toluene.

16. Thus, as on the priority date of the Patent, i.e. 11 June 1998, the technique of recrystallisation, methods of solvent selection and solvent properties of heptane, toluene and tetrahydrofuran were known.

17. The Opponent therefore believes that given the prior art, the alleged invention claimed in the Patent comprising the recrystallisation of Form 1 of Efavirenz using tetrahydrofuran-heptane followed by heating the product obtained does not involve any inventive step but can easily be obtained by a person skilled in the art.

GROUNDS

18. The Opponent believes that the claim granted in the Patent is not patentable in India on the following grounds:

    A. Section 25(2)(e)—that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to what the matter published as mentioned in clause Section 25(2)(b).

    B. Section 25(2)(f)—that the subject of any claim of the complete specification is not an invention within the meaning of this Act.

    C. Section 25(2)(h)—that the Patentee has failed to disclose to the Controller the information required by Section 8.

A. The claim granted is obvious to a person skilled in the art under Section 2(j), 2(ja) and should be denied under Section 25(2)(e).

19. The Opponent submits that Claim 1 as granted fails for lack of inventive step. Section 2(j) of the Act defines an invention as a new product or a process, involving an inventive step and capable of industrial application. Section 2(ja) of the Act defines an inventive step as "a feature of an invention that involves technical advance as compared to the existing knowledge … and that makes the invention not obvious to a person skilled in the art".

20. Sub-sections (j) and (ja) of Section 2 of the Act thus require an Applicant to show that the alleged invention involves a technical

advance and that it is not obvious to a person skilled in the art. These requirements are laid down to ensure that patents, which result in a monopoly, are granted only to genuine inventions.

21. Section 25(2)(e) of the Act provides a ground of opposition on the ground that the alleged invention is obvious and does not involve an inventive step having regard to matter published in Section 25(2)(b). Section 25(2)(b) sets out that such published matter includes matter published in India or elsewhere in any document before the priority date of the alleged invention.

22. The Patentee has claimed a recrystallisation process to prepare Form 1 of Efavirenz by heating Form 4 of Efavirenz, which is obtained by using a combination of heptane and tetrahydrofuran as solvents.

23. The Opponent submits that the use of toluene-heptane as solvents to crystallise Efavirenz was already known before the priority date claimed for the alleged invention. Lilian Radesca, *et al*, "Synthesis of HIV-1 Reverse Transcriptase Inhibitor DMP 266", Synthetic Communications, 27(24), 4373–4384 (1997), a copy of which is hereto annexed and marked as "**Exhibit E**", at 4382–4383 teaches the use of heptane-toluene in a 85:15 mixture to crystallise Efavirenz. The product obtained has a melting point of 139–141 °C.

24. WO9804535 published on 5 February 1998, a copy of which is hereto annexed and marked as "**Exhibit F**", discloses the use of heptane-toluene to crystallise Efavirenz. [*See* example 3, at internal page 32 and example 5, at internal page 34]. More specifically, example 5 at internal page 34, discloses use of heptane-toluene in an 85:15 proportion followed by drying in a vacuum oven at 65°C to obtain Efavirenz. WO9804535, i.e. Exhibit E at internal page 20, also

discloses that suitable aprotic solvents that can be used for the synthesis of benzoxazinones include tetrahydrofuran.

25. As stated above, Exhibit A describes the recrystallisation process using a two-solvent system. Exhibits B and C teach solvent selection methods, which can be used to find alternate solvents. More particularly, the solvent properties listed in Exhibit C disclose that tetrahydrofuran, a known aprotic solvent, exhibits a lower relative ability to donate protons (*See* Exhibit C, internal page 295), a lower boiling point, a greater dielectric constant, higher polarity and a higher solubility parameter (*See* Exhibit C, internal page 300) than toluene. Because of the higher dielectric constant, higher polarity and higher solubility parameter, tetrahydrofuran would better interact with the impurities in the Efavirenz solution thereby facilitating crystallisation of Efavirenz. At the same time, the lower relative ability of tetrahydrofuran to donate protons means that it will not significantly interact with the solute molecules of Efavirenz. The lower boiling point of tetrahydrofuran means that the recrystallisation can be conducted at a lower temperature. Further, Exhibit D, as on the priority date of the Application, classifies tetrahydrofuran and toluene as Class 3 and Class 2 solvents respectively. Thus, the toxicity of tetrahydrofuran was considered to be lesser than that of toluene.

26. The Opponent submits that recrystallisation and the selection of recrystallisation solvents is a matter of routine detail known to persons skilled in the art and determinable by a routine trial and error process. Further, given the prior art referred to above, it would have been obvious to a person skilled in the art to conclude that tetrahydrofuran was a good alternate solvent for recrystallisation of Efavirenz in the processes described in Exhibits E and F. This substitution does not

constitute any technical advance and is obvious to a person skilled in the art.

27. The Opponent states that a person skilled in the art can easily determine the specific ratio of tetrahydrofuran-heptane by a routine trial and error method. Further, the temperature at which the compound is to be heated to convert Form 4 to Form 1 is also easily determinable by a person skilled in the art.

28. The Opponent states that the Chennai Patent Office in *M/s Novartis AG, Switzerland v. M/s. Cancer Patients Aid Association, India*, Application No. 1602/MAS/1998, a copy of which is hereto annexed and marked as **"Exhibit G"**, held that a patent document which disclosed that acid addition salts are obtained in a "customary manner" would anticipate a later alleged claim of a particular salt form of the compound. The decision also holds that for this reason, the alleged claim would also be defeated on the ground of obviousness. Thus, as the present alleged invention comprises nothing more than recrystallising Form 1 of EFV using the customary manner of recrystallisation and selection of recrystallisation solvents, the Opponent submits that the granted claim does not meet the requirement of inventive step.

29. The Opponent therefore states that the claim fails to meet the requirement of inventive step and is therefore not patentable.

B. The granted claim is mere use of a known process under Sections 3(d) and 25(2)(f).

30. Section 3(d) of the Act excludes from patentability mere use of known processes unless the process results in a new product or employs at least one new reactant.

31. The Opponent states that given Exhibits E and F, the process of crystallising Efavirenz by using toluene-heptane is known. Undoubtedly, tetrahydrofuran is a known reactant (*See* Exhibits B, C and D) and has been disclosed by the Patentee itself at internal page 18 of Exhibit F as an aprotic solvent that can be used in the synthesis of Efavirenz. Tetrahydrofuran is thus not a new reactant.

32. The granted claim thus is a known process and does not employ any new reactant. Neither does the process result in the formation of any new product. Therefore, the granted claim is not patentable under Section 3(d) of the Act.

C. The Patentee has failed to provide sufficient information as required under Section 8.

33. Section 8 of the Act requires an Applicant to submit a statement setting out detailed particulars of the same or substantially the same invention at the time of the application or within such time as the Patent Controller may allow. Section 25(2)(h) provides a ground of opposition for non-disclosure of sufficient information required under Section 8.

C.1. Failure to file statement under Section 8

34. The Opponent states that the Patentee had filed the Application on 27 October 2000 but failed to file the particulars of corresponding applications filed outside India within the prescribed time period.

35. An inspection by an agent of the Opponent of the Patent and the documents pertaining thereto under Rule 74A of the Patent Rules, 2003 revealed that it was only vide a petition under Section 138 of the

Patents Act, 1970 dated 11 June 2003 for which payment was made vide a cheque dated 21 July 2003 that the Patentee submitted these details and sought condonation of delay. However, the Opponent bona fide and reasonably believes that the Controller has not passed an order condoning the delay. The Opponent believes that there has been a failure on the part of the Patentee in submitting information required under Section 8 as prescribed. The Patent therefore ought to be revoked on the ground of failure to provide information relating to of the same invention. The Patent therefore ought to revoked on ground of non-compliance with requirements of Section 8 of the Act.

C.2. Failure to provide details of applications relating to substantially same inventions.

36. The Opponent further submits that pursuant to an international application under the PCT, bearing No. WO9964405 designating India. WO9964405 claims Forms 1, 2, 3, 4 and 5 of crystalline Efavirenz, a benzoxazinone. The Application discloses and claims recrystallisation of Form 1 of Efavirenz using a two solvent system of tetrahydrofuran-heptane followed by subsequent heating to 80–100°C.

37. The Opponent believes that the Patentee, who is admittedly an assignee of DuPont Pharmaceuticals Company, has failed to disclose that DuPont Pharmaceuticals Company filed an application in the United States on 11 April 1997 based on a provisional application dated 16 December 1996 for which it was granted a US patent bearing no. 5,932,726, a copy of which is hereto annexed and marked as **"Exhibit H"**. On 15 December 1997, the corresponding international application under the PCT bearing No. WO9827073, a copy of which is hereto annexed and marked as **"Exhibit I"**, was filed claiming priority from the application filed in the United States on 16 December 1996. This PCT application was published on 25 June 1998, merely

two weeks after the filing of the present application. Exhibits I and J pertain to a substantially same invention, i.e. asymmetric synthesis of benzoxazinones. More particularly, example 7 at column 41 of Exhibit H and internal pages 48–49 of Exhibit I discloses use of the tetrahydrofuran-heptane and subsequent drying in vacuo at 90–100°C to obtain crystalline Efavirenz with a melting point of 139–141°C. This is precisely the scope of the claim as granted in the Patent.

38. Similarly, the Patentee has also not disclosed that on 2 April 1998, DuPont Pharmaceuticals Company filed an international application under the PCT bearing no. WO9845278, a copy of which is hereto annexed and marked as **"Exhibit J"**. This application discloses that tetrahydrofuran-heptane is the preferred solvent in the final cyclization step of Efavirenz. Example 7 at pages 58–59 of Exhibit J discloses use of the tetrahydrofuran-heptane and subsequent heating at 90–100°C to obtain crystalline Efavirenz with a melting point of 139–141°C. This is precisely the scope of the claim as granted in the Patent.

39. The Patentee has thus failed to provide sufficient information relating to applications for substantially same inventions that it is pursuing in other countries. The Patent therefore ought to be revoked for non-disclosure of sufficient information pertaining to a substantially same invention and consequent non-compliance with statutory requirements.

40. The Opponent furthers request a hearing by the Opposition Board.

41. The Opponent states that the grant of the patent was published in the Patent Official Journal on 3 February 2006. Therefore, this opposition has been filed within the time limit prescribed.

RELIEFS CLAIMED

42. Given the foregoing, the Opponent hereby humbly requests that the Patent Office revoke the Patent on the following grounds:

A. That the invention so far as claimed in the Patent is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in Section 25(2)(b);

B. That the subject of the claim of the Patent is "mere use of known process which does not result in a new product or employ any new reactant" and therefore not patentable under Section 3(d) of the Act; and

C. That the Patentee has failed to disclose to the Controller information required by Section 8 of the Act.

Respectfully submitted,

On Behalf of the Delhi Network of Positive People,

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Date