

The Patents Act, 1970

IN THE MATTER OF:

A representation under section 25(1) of The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005 (“the Act”) and Rule 55 of The Patents Rules 2003 as amended by the Patents (Amendment) Rules 2005 (“the Rules”) by Indian Network for People Living with HIV/ AIDS (“INP+”) and Positive Women Network (PWN+) (“the OPPONENTS”)

And

IN THE MATTER OF:

Indian Application No. 2485/DEL/1998, filed on 24th August 1998 by Boehringer Ingelheim Pharmaceuticals. Inc (“the APPLICANT)

STATEMENT OF OPPOSITION

1. The “Opponents hereby make a representation by way of opposition under Section 25(1) of the Patent Act 1970, as amended by the Patents (Amendment) Act, 2005 (the “Act”) against the grant of patent application, titled: “Pharmaceutical Suspension Comprising Nevirapine Hemihydrate”, filed by the Applicant Boehringer Ingelheim Pharmaceuticals. Inc (the “Applicant”), on 24th August 1998, bearing the Indian patent application No. 2485/DEL/1998 (the “Application”) and the Application was published for opposition in the Official Journal of the Patent Office on 4th March

2005 in Vol X, a copy of which is attached as **[Exhibit 1]**. It is understood to have not yet been granted.

2. The Opponents are community based, non-profit organisations representing the needs of people living with HIV/AIDS (“PLHAs”).The Opponents, Indian Network for People Living with HIV/ AIDS (“INP+”) is registered as Society No. SI. No. 231/1997 under Section 10 of the Tamil Nadu Societies Registration Act, 1975 (Tamil Nadu), Act 27 having its registered address at Flat # 6, Kash Towers,# 93, South West Boag Road,T.Nagar,Chennai.- 600017. The Positive Women Network is registered as Society No.SL.No. 396/1998 under the Tamil Nadu Societies Registration Act, 1975 (Tamil Nadu) Act 27, having its registered address at No.9/5, Shanthi Apartments, Avenue Road, Nungambakkam, Chennai - 600 034.
3. The Opponents represent and provide support for 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. INP+ aims to improve the quality of life of people living with HIV/AIDS and give them a sense of belonging, political empowerment and strength of spirit. Positive Women Network is an organization formed by women living with HIV/AIDS (WLHA) to address the need for a support system and to improve the quality of life of women living with HIV and their children in India. Of particular concern to the Opponents is the impact of the new product patent regime on PLHAs’ access to safe, effective and affordable HIV/AIDS treatments

4. The Application was filed at the Patent Office in Delhi, therefore, the Patent Controller has the jurisdiction to hear this pre-grant opposition in Delhi. Opponents hereby request a hearing as per provisions under Rule 55(1) of the Patent Rules, 2005.

The Patent, If Granted, Will Cause Significant Public Harm

5. The present Application relates to a treatment for HIV-1 infection, which has affected a large populace in India and much of the developing world. Although, there have been treatments available for HIV, millions of people have been unable to afford the drugs. Patent protections granted to treatments for HIV only exacerbate this problem. The 20 year monopoly period granted to a patent owner allows the owner to set prices at levels impossibly beyond reach for the vast majority of those who are in desperate need of treatment.
6. In order to comply with the TRIPS obligation, India for the first time introduced a 20 year product patent regime through the Patents (Amendment) Act, 2005. However, the Parliament introduced Section 3(d) in order to prevent frivolous being granted for mere incremental additional to an active ingredient.. In this Application, the original patents for the active ingredients of this drug was granted prior to 1995, when India first incurred its obligations under the WTO. The “improvement” at issue is the addition of pharmacologically inactive ingredients and the use of nevirapine hemihydrate having a particle size between 1 and 150 microns which does nothing to improve the drug’s efficacy. Granting a patent to the current Application will do nothing but further enrich the Applicant at the expense of human lives.

7. The Opponents humbly submit that the obligation to uphold the true intention of the Parliament to safeguard the public health interests of its citizens rests with the Patent Office, as it is this Office that ultimately examines the present Application and interprets the applicable law and makes the decisions that will determine whether millions of people will have access to essential medicines.

The Alleged Invention Is Not Patentable Under The Act

8. The Application is for a pharmaceutical suspension comprising nevirapine hemihydrate, which is nothing but an aqueous suspension of the hemihydrate form of nevirapine, a pseudopolymorph that can exist in anhydrous and hemihydrate form. The hemihydrate form of nevirapine when placed in an aqueous suspension is suitable for paediatric use. The Applicant has failed to meet its burden of showing that the alleged invention described in the Application is entitled to a patent under the Act as, the present Application relates to nothing more than using the hemihydrate form of nevirapine particles in a pharmaceutical composition consisting of known pharmaceutical additives. Nevirapine is known to have existed prior to 1995 and is known through US patent No. 5366972 [**Exhibit 2**], US patent No. 5620974 [**Exhibit 3**], US Patent No. 5569760 [**Exhibit 4**]. Also the prior art reference Angel et al [Proc. 50th Annual Meeting of the Electron Microscopy Society of America, pp1326-1327 (1992) [**Exhibit 5**] points to the existence of the hemihydrate form of nevirapine. The Application, makes a specific claim as to the use of nevirapine hemihydrate particles which are of the size 1-150 microns that can be milled so that the particle size will fall within in this range. The pharmaceutical additives used in the

formulation are the conventional additives widely used in the industry and provide no added therapeutic advantage.

9. Despite this, the Applicant, nonetheless claims that the alleged invention is patentable. The Applicant's claims can be summarised as follows:

- a. Claim 1 is a method for preparing an aqueous suspension of nevirapine which method comprises admixing nevirapine hemihydrate, having particle size between about 1 and 150 microns;
- b. Claim 2 is a pharmaceutical composition consisting essentially of nevirapine hemihydrate, having particle size between about 1 and 150 microns, and water;
- c. Claims 3, 4 is a pharmaceutical composition consisting essentially of conventional pharmaceutical additives and nevirapine hemihydrate of a specified range wherein the nevirapine particle size is between 1 and 150 microns in diameter
- d. Claim 5 is for the use of nevirapine hemihydrate for preparing a pharmaceutical composition for treatment of HIV-1 infection;
- e. Claim 6 is an omnibus claim relying on the earlier claims.

10. Thus, the claims of the Application all relate to the use of the known nevirapine hemihydrate having a particle size between 1-150 microns in a pharmaceutical composition consisting essentially of water, and well known pharmaceutical additives.

However, merely using the hemihydrate form of nevirapine wherein particle size is between 1 and 150 microns in a pharmaceutical composition is insufficient to render the alleged invention patentable under the Act. This is because the mere use of a particle size of 1-150 microns of hemihydrate form of nevirapine in a pharmaceutical composition consisting of conventional pharmaceutical additives and/or water is: (i) at most, a mere “discovery” of a *new form* of a known substance and is thus not an invention under Section 3(d) of the Act; (ii) a “mere admixture” and is thus not an invention under Section 3(e) of the Act; (iii) anticipated by the disclosures contained in the US patent 5620974 and thus lacks novelty; and (iv) obvious to one skilled in the art. Each of these separate and independent grounds for denying the present Application is discussed in further detail below.

The Alleged Invention Is Not An Invention Under Section 3(d) Of The Act Because It Is The Mere “Discovery” Of A New Form Of A Known Substance.

11. The alleged invention is not patentable under the Act because it is, at most, the mere “discovery” of a new form of a known substance. Under Section 3(d) of the Act, the “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 an invention within the meaning of the Act. The Explanation to Section 3(d) states, “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,” (emphasis added). The alleged invention claims to be and is in fact nothing more than an aqueous suspension of an *hemihydrate form of a known*

substance having a particle size of 1-150 microns, and the Applicant has made no attempt to meet its burden of showing that this combination results in a product that results in an “enhancement of the known efficacy,” it is not an invention within the meaning of the Act under Section 3(d).

12. The Applicant unequivocally admits that nevirapine is a known substance and that the hemihydrate form of nevirapine exists in a stable form. The Applicant states, “Nevirapine, or 11 cyclopropyl-5, 11 dihydro-4-methyl-6H- dipyrido [3,2-b:2',3'-e] [1,4] diazepin-6-one, is a known agent for the treatment of infection by HIV-1 reverse transcriptase. Its synthesis and use are described in various publications including, inter alia, US Patent No. 5,366,972, US Patent No. 5620974 and US Patent No. 5569760”. Added to this the Applicant states “Angel et al [Proc. 50th Annual Meeting of the Electron Microscopy Society of America, pp1326-1327 (1992)] have disclosed that nevirapine exists as the hemihydrate stable form.....” Furthermore, the US Patent No.5,620,974 states that “the pharmaceutical preparations containing nevirapine can be prepared in a liquid dosage form, for example solutions, suspensions, emulsions and the like. It goes on to state that “pharmaceutical preparations may contain conventional adjuvants such as preservatives, stabilizers, emulsifiers, flavour improvers...” Thus, it is beyond debate that nevirapine is a known substance and the pharmaceutical preparation consists of only standard excipients.

13. Likewise, the Applicant admits that the pharmaceutical composition comprises of “conventional pharmaceutical additives, such as but not limited to, suspending agents and/or viscosity thickening agents such as, for example cellulose based polymers or synthetic polymers, preferably cross linked polymers such as carbomers; wetting agents such as,

for example polyethylene oxides or polyoxyethylene sorbitan fatty acid esters (polysorbates); sweetening or flavouring agents, such as sucrose; and preservatives, such as for example parabens.” Far from being new or unknown substances these are standard excipients known and used widely by the pharmaceutical industry in pharmaceutical preparations and the Applicant cannot claim invention over pharmaceutical compositions consisting of such conventional additives and nevirapine.

14. As the foregoing shows, all of the substances contained in the present Application are known. Nevertheless, the Applicant in Claim 1 purports to stake ownership over the following: “A pharmaceutical composition comprising: (i) a method for preparing an aqueous suspension of nevirapine which method comprises admixing nevirapine hemihydrate, having particle size between about 1 and 150 microns; (ii) a pharmaceutical composition consisting essentially of nevirapine hemihydrate, having particle size between about 1 and 150 microns and/or water; (iii) a pharmaceutical composition consisting essentially of conventional pharmaceutical additives and nevirapine hemihydrate of a specified range wherein the nevirapine particle size is between about 1 and 150 microns in diameter. It is abundantly clear that each of the substances in the claimed combination is a known substance. As such, under Section 3(d) of the Act, the combination of these known substances can be considered an invention only if the Applicant can show that the combination results in the “enhancement of the known efficacy” of the product. Applicant has failed to meet this burden.

15. In order to meet its burden under Section 3(d), the Applicant is required to present evidence that the claimed invention represents an enhancement in the known efficacy over the previously known substance. The Applicant does not and cannot satisfy this

requirement. The only active ingredients in the claimed invention is nevirapine and the excipients in the pharmaceutical composition do not have any added therapeutic advantage and the therapeutic efficacy of the active ingredients were already known and disclosed in the US Patent No. 5620974. Nowhere in the Application does the Applicant even attempt to show that the pharmaceutical composition consisting of nevirapine hemihydrate along with conventional pharmaceutical additives represents an improvement in efficacy over the earlier patent.

16. The sole improvement that the Application discloses with respect to the hemihydrate form of nevirapine in the pharmaceutical composition is with regard to the particle size, which is between about 1 and 150 microns in diameter and can be obtained through the well known process of milling. The change in particle size is insufficient to meet the “known efficacy” requirement under Section 3(d) and merely using a hemihydrate form of nevirapine in a pharmaceutical suspension does not merit a patent as nevirapine hemihydrate is known to have existed prior to this application and efficacy in the field of pharmaceuticals is formally defined as “the capacity of an agonist to initiate a response once it occupies receptor sites”. However it must be noted that ‘clinical efficacy’ is also used to identify the efficacy of a drug to treat the claimed indications in real patients. In view of such standard definitions, the claims made in Application do not even get close to meeting these required standards of “efficacy”.

17. This alleged “improvement” bears no relation to the ultimate therapeutic efficacy of the active ingredient and it is common knowledge to reduce the particle size of the active

ingredient in a suspension, which has no added therapeutic effect compared to the active ingredient. The Applicant has put forth no evidence to show that the efficacy is greater than that of nevirapine disclosed in the earlier patents, moreover there is nothing to say that earlier disclosed nevirapine might not have been of a different particle size. Parliament, in its considered wisdom, could have drafted Section 3(d) so that the relevant standard was not an improvement in the “known efficacy”. Given that Parliament declined to do so, the alleged “improvement” claimed in the present Application fails to pass the requirements, and cannot be considered an invention under Indian law.

The Alleged Invention Is A Mere Admixture And Is Unpatentable Under Section 3(e) Of The Act.

18. Under Section 3(e) of the Act, “a substance obtained by the mere admixture resulting only in the aggregation of the properties of the components thereof” is not an invention within the meaning of the Act. For all of the reasons hereinabove stated, the present Application fails on this ground as well. The only active ingredient in the alleged invention was disclosed in the US patent No. 5,620,974 and the rest of the formulation constitutes conventional pharmaceutical additives that add no efficacy to the final product. As such, the pharmaceutical composition under the present Application is nothing more than the “aggregation of the properties” of its constituent components. For these reasons, the present Application is a mere admixture and not an invention under Section 3(e) of the Act.

The Alleged Invention Is Anticipated by A Prior Publication.

19. Claims 1-2 and Claims 3-4 of the present Application fail on the additional ground that they lack the requisite novelty for patentability. Section 2(l) of the Act defines a “new invention” as “any new invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification.” Thus, if a publication prior to the present Application discloses the claimed invention, then the Application lacks novelty and must be rejected.

20. In the present Application, the prior art reference (Angel et al, 50th Annual Meeting of the Electron Microscopy Society of America, 1992, 132-1327) discloses that nevirapine exists as the hemihydrate stable form and as the anhydrous metastable form. Further, the US patent 5,620,974 already discloses pharmaceutical compositions comprising nevirapine for treating AIDS and disorders associated with HIV-1. It goes on to state “when the compounds of the present invention are to be administered by oral route, they may be administered as medicaments in the form of pharmaceutical preparations which contain them in association with a pharmaceutical preparations, with a compatible pharmaceutical carrier material. Such carrier material can be an inert organic or inorganic material suitable for oral administration. Examples of such carrier materials are water....” It further goes on to state “ The pharmaceutical preparations can be prepared in a conventional manner and finished dosage forms can be solid dosage forms, for example, tablets, dragees, capsules and the like or liquid dosage forms, for example solutions, suspensions, emulsions and the like...Further, the pharmaceutical preparations may contain conventional adjuvants such as preservatives, stabilizers, emulsifiers, flavour improvers, wetting agents, buffers....” From the disclosures made in the US patent

5,620,974, it cannot be ruled out that the oral nevirapine composition using water and/ or other pharmaceutical additives does not contain nevirapine hemihydrate. It would be immediately evident to one skilled in the art that the disclosures made in the US patent 5,620,974 readily anticipates the claims made in this Application. Therefore, Claims 1-2, Claims 3-4 and Claim5 of the present Application all fail for lack of novelty.

The Alleged Invention Is Obvious To A Person Skilled In The Art

21. For all of the reasons stated above, Claims 1-2, Claims 3-4 and Claim 5 of the present Application also fail because they lack the inventive step required for patentability and are obvious to someone skilled in the art. It is well known from the US Patent No. 5620974 that nevirapine could be delivered in a pharmaceutical suspension. From the prior art disclosed by Exhibit 4 it was well known that anhydrous form of nevirapine could not be used to make a composition as it turned from this less stable form into the more stable nevirapine hemihydrate but experienced a runaway crystallisation when it did, dropping out of solution. But at the same time it was very well known that nevirapine in its crystalline form could exist in anhydrous or hemihydrate form and it is known practice that if one form was non conducive in making a pharmaceutical suspension, it would be obvious to try the other form. Therefore, any person skilled in the art would obviously attempt to add nevirapine hemihydrate to water in order to see what happened if hemihydrate is directly used to make a pharmaceutical composition, and would have obviously experimented with different sizes of particles as obvious and routine experimentation. It is disclosed by the Application that the result was unexpected and the fact that one form is stable within a certain range is in effect a bonus result. Moreover, the pharmaceutical excipients used in the composition along with nevirapine hemihydrate

are nothing more than standard excipients widely known and used in the pharmaceutical industry to prepare pharmaceutical compositions. Further, the Applicant admits that the excipients are widely used by the pharmaceutical industry. Thus it is quite clear that it was an obvious choice for any one skilled in the art to use hemihydrate form directly in the pharmaceutical composition rather than using an anhydrous form and there were hardly any other alternatives. Under Section 2(ja) of the Act, “inventive step” is defined as “a feature of an invention that involves technical advance as compared to the existing knowledge...that makes the invention not obvious to a person skilled in the art.”

22. For the reasons already stated, it would have been obvious to a person skilled in the art, given the disclosures contained in the US patent 5620974 to easily arrive at the composition claimed in the Application as only standard excipients known in the art is contained in the pharmaceutical composition.

CONCLUSION

23. Given all of the foregoing, Opponents hereby humbly request that the Patent Office reject the Application on the following grounds:

- a. The alleged invention is a “mere discovery of a new form of a known substance” and thus not an invention under Section 3(d) of the Act;
- b. The alleged invention is a “mere admixture” and thus not an invention under Section 3(e) of the Act;
- c. Claims 1-5 and of the present Application fail for lack of novelty; and

d. Claims 1-5 in the present Application fail for lack of inventive step.

24. Opponents further request that the Office grant a hearing as per Rule 55(1) of the Patent Rules.

Dated 9th May 2006

For and behalf of the Indian Network for People Living with HIV/ AIDS (INP+)

For and behalf of the Positive Women's Network (PWN+)

Our address for service in connection with these proceedings is: -

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To:

The Controller of Patents

The Patent Office, NEW DELHI