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 2006 ("the Rules") by Indian Network for People Living with HIV/ AIDS ("INP+"), the Delhi Network of Positive People (DNP+) and the Network of Maharastra by People Living with HIV/AIDS (NMP+) ("the OPPONENTS")

And

IN THE MATTER OF:

Application No. IN/PCT/2002/1243/ MUM filed on 11th September 2002 by Abbott Laboratories, USA ("the APPLICANT)

STATEMENT OF OPPOSITION

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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 "Crystalline Pharmaceutical", filed by the Applicant Abbot Laboratories, USA (the "Applicant"), on 11 September 2002, bearing the Indian patent application No. IN/PCT/2002/1243/MUM (the "Application") **Exhibit 1.** The Application was published for opposition in the

Official Journal of the Patent Office on 4th March 2005 in Vol V, a copy of which is attached as **Exhibit 2** and 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), having its registered address at Flat # 6, Kash Towers, # 93, South West Boag Road, T.Nagar, Chennai - 600017. The Delhi Network of Positive People ("DNP+") is registered as Society No. S-52850 under the Societies Registration Act XXI 1860, having its registered address at House No. 136, Village Neb Sarai, New Delhi, 110068. The Network of Maharastra by People Living with HIV/AIDS (NMP+)is a registered society having its address at NMP+, Kashiba Shinde Sabhagraha,Waghere Vasti, Pimpri Gaon, Pimpri, Pune.

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. 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 treatment.

4. The Application was filed at the Patent Office in Mumbai, therefore, the Patent Controller has the jurisdiction to hear this pre-grant opposition in Mumbai. The

Opponents hereby request a hearing as per provisions under Rule 55(1) of the Patent Rules, 2006.

5. The present Application relates to a treatment for HIV, a disease which has affected a large population in India and much of the developing world. Although there are treatments available for HIV, millions of people are unable to afford such drugs. Patent protections granted to treatments for HIV only exacerbate this problem. The Opponents submit that the obligation to uphold the true intention of Parliament and to safeguard the public health interests of its citizens rests with the Patent Office.

6. The Application is for the various crystal forms (hydrated, solvated, non-solvated, de-solvated) of the known compound Lopinavir, which was disclosed in an earlier application, US Patent No. 5914332, issued 22 June 1999, **Exhibit 3**. The Application also claims substantially pure forms of the various Lopinavir crystals with respective infrared spectrum and x-ray diffraction reading. The Applicant also asserts that the claimed invention of crystalline forms helps to purify or isolate Lopinavir which enables the preparation of pharmaceutical compositions for its administration.

7. In particular, the Applicant's claims can be summarised as follows:

    a. Claims 1-4 relate to a crystalline hydrated form of Lopinavir, and its substantially pure form including a specific solid state infrared spectrum.

    b. Claims 5-6 cover a solvated crystalline form of Lopinavir and a substantially pure form of Lopinavir, with a specific solid state infrared

spectrum range of 1661-1673 cm-1, 1645-1653 cm-1 and 1619-1629 cm-1.

c. Claims 7-10 are for a crystalline form of Lopinavir and a substantially pure form of Lopinavir, with a peak in the solid state infrared spectrum at a position within the range of 1655-1662 cm-1 and 1636-1647 cm-1.

d. Claims 11-14 cover a solvated crystalline form of Lopinavir and a substantially pure form of Lopinavir, with a specific solid state infrared spectrum range of 1655-1662 cm-1, 1636-1647 cm-1.

e. Claims 15-23 are for non-solvated crystalline forms of Lopinavir and its substantially pure form, with a specific peak in the solid state infrared spectrum and x-ray diffraction pattern values.

8. The Opponents have studied the Application and believe that the Application does not meet the requirements of patentability as required under the Act. The Opponents firmly believe that the claims made by the Applicant are not patentable under the following grounds of s25(1) of the Act:

a) Section 25(1)(f) – that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act, in particular under Sections 3(d).

b) Section 25(1)(b)(ii) - that the invention so far as claimed in any claim of the complete specification has been published before the priority date… in India or elsewhere in any other document:

c) Section 25(1)(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 the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim.

d) Section 25(1)(h) – that the applicant has failed to disclose to the Controller the information required by Section 8 or has furnished the information that in any material particular was false to his knowledge.

Accordingly, as permitted under s25(1) of the Act and Rule 55(1) of the Rules, which allow an opposition to be filed by any person after publication but before the grant of a patent, the Opponents submit their opposition on the grounds set out below. Furthermore, as the Application was filed at this Patent Office (Mumbai), the Patent Controller of this office has the authority to hear and decide on this opposition.

GROUNDS

The grounds for opposing this Application are set out as follows:

Claims 1-23 of the Application are not inventions under sections 3(d) and 25(1)(f) of the Act

9. The inventions claimed are not patentable under the Act because they are, at most, a mere "discovery" of a new form of a known substance. Under s3(d), 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 s3(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). Claims 1-23 in the Application are nothing more than polymorphic forms of the known substance Lopinavir. The Applicant has made no attempt to meet its burden of showing that the various claimed crystalline forms of Lopinavir i.e., *hydrated, solvated, non-solvated or de-solvated* forms, result in an "enhancement of the known efficacy", and therefore cannot be considered inventions under s3(d). Furthermore, the substantially pure forms of the various crystalline forms of Lopinvavir claimed by the Applicant are also not patentable under the Act as s3(d) specifies that pure forms of a known substance are to be considered to be the same substance.

10. The Applicant unequivocally admits that Lopinavir is a known substance and the earlier disclosure made in US Patent No. 5914332, **Exhibit 3**, shows the process of preparing an amorphous form of Lopinavir. It is well known in the pharmaceutical industry that a solid form of an organic compound may exist in crystalline and/or amorphous forms. In a crystalline form, a drug may exist in one of seven different crystal states and the particular crystal state that a solid drug assumes depends upon the choice of the solvent that is used for re-crystallisation and/or the choice of the solvent pair used for precipitation**.**

11. In order to meet its burden under s3(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 active ingredient, Lopinavir, is already known and the Applicant fails to show that the crystalline forms have any added therapeutic advantage or efficacy over the amorphous form of Lopinavir, which was disclosed in the US Patent No. 5914332. Consequently, the crystalline form must be considered to be the "same substance" as the original Lopinavir compound under s3(d) of the Act. The different polymorphic forms may be considered the same as stated in the U.S. FDA's Draft Guidance on Polymorphs, **Exhibit 4,** wherein three "decision trees" are given that provide guidance as to whether a different polymorphic form will ultimately affect drug performance. As shown in the very first "decision tree," if all known polymorphs exhibit the same solubility or are all highly soluble, "no further test or polymorphic acceptance criterion" is necessary. This is because other factors that may vary in different polymorphic forms, such as stability, particle shape, flowability, compactability, hygroscopicity, etc. can be controlled and accounted for during the manufacturing process to produce a product that has equal efficacy to a known drug product utilising a different polymorph. Thus, there is no scientific basis for one to conclude that using a different drug substance polymorph from the original drug product would preclude a later version of the drug from demonstrating drug product manufacturability, bioequivalence, and stability. In the current Application, the Applicant makes no mention of possible varying solubilities between the various crystalline forms of Lopinavir. The Applicant only shows infrared red and x-ray

diffraction readings of the various forms of Lopinavir, which is nothing more than a mere method of identifying the various crystalline forms of Lopinavir.

12. Efficacy in the field of pharmaceuticals is defined in Bowman's 'Dictionary of Pharmacology' (1986) as "the capacity of an agonist to initiate a response once it occupies receptor sites". Another useful and more detailed definition is that provided in the attached **Exhibit 5**, which broadly defines efficacy as "referring to the capacity of a drug to produce an alteration in a target cell/organ after binding to its receptor." **Exhibit 6** also states that efficacy is related to 'intrinsic efficacy', which broadly means "the property of a drug that determines the amount of biological effect produced per unit of drug-receptor complex formed." For a definition of 'intrinsic efficacy' see **Exhibit 6**. In view of such standard definitions, the claims made in the Application do not meet these required standards of "efficacy", and fail to mention any improvement over the already known form of Lopinavir. Therefore, the alleged polymorphic forms of Lopinavir in the present Application fail to pass the standard of patentability under Indian law.

Claims 1-23 of the Application are not new inventions for the purpose of sections 25(1)(b)(ii) and 2(j)

13. Claims 1-23 in the Application fail on the additional ground that they lack the requisite novelty for patentability. Section 2(j) of the Act defines an invention as a "new product". Section 25(1)(b)(ii) clarifies this definition by providing that where the invention claimed has been published before the priority date of the claim in India or elsewhere, the alleged invention is not patentable. Thus, if a publication prior to

the present Application discloses the claimed invention, then the Application lacks novelty and must be rejected.

14. Although it is true that the crystalline forms of the organic compound, Lopinavir, were never specifically disclosed in the US patent No. 5914332, it is not always necessary that all forms of the compound be actually disclosed in the prior art in order to make out a showing of anticipation: "For a prior publication to have prejudicial effect, …it is not necessary for the starting compound or process variant to be given special prominence. The essential point is what a person skilled in the art, carrying out the invention, could be expected to deduce from it." (Bayer/Diastereomers, T12/81 (1982) OJEPO 296), **Exhibit 7.** Thus, even if a prior publication does not expressly disclose in words one or more elements of a patent's claims, it may nevertheless be anticipating if a person of ordinary skill in the art could have combined the publication's description of the invention with his/her own knowledge to make the claimed invention. It is also true that where the claims of a later patent are subsumed but not specifically disclosed by a prior art reference, the later claims may nevertheless be found to have been anticipated by the prior disclosure. In the present Application, the amorphous form of Lopinavir was disclosed prior to this application, but any person of ordinary skill in the art could have easily combined the known form of Lopinavir with common knowledge, using various solvents to crystallise Lopinavir. Thus, the claims made in the Application would have been easily anticipated by the prior disclosure and therefore the Application lacks novelty.

Claims 1-23 of the Application are not patentable under sections 2(j), 2(ja) and 25(1)(e) of the Act as they would have been obvious to a person skilled in the art

15. Claims 1-23 in the Application also fail because they lack the inventive step required for patentability and are obvious to someone skilled in the art. Although the US Patent No.5914332 discloses Lopinavir only in the amorphous state, obtaining the crystalline forms of Lopinavir cannot be considered as sufficiently inventive or involving a technical advance. It is well known in the art how to obtain crystalline forms of a given compound using routine experiments. A solid form of an organic drug may exist in amorphous or crystalline form. In a crystalline form, a drug may exist in different crystal states. However, a particular crystalline state depends upon the choice of the solvent that is used for recrystallisation and/or the choice of the solvent pair used for precipitation as shown by the earlier patent PCT/US98/12474, published on 23 December 1998, **Exhibit 8.** Using this widely available knowledge a person skilled in the art could easily arrive at the crystal forms described in the Application.

16. An ordinary skilled person in the art would use or experiment with a range of solvents that are commonly used in re-crystallisation to achieve this end. Solvents like water, ethanol, ethyl acetate, chloroform, acetyl nitrite, isopropanol, propylene glycol etc, mentioned in the Application are routine solvents used in the re-crystallisation (*Vogels, 1989 Textbook of practical organic chemistry, London: Longman Scientific & Technical ; New York : Wiley)* **Exhibit 9**. Crystallisation commonly involves routine trial and error before results are achieved. The process of crystallisation used is conventional and capable of being effected with a variety of solvents and in a number of different ways. Generally, purifying and crystallising an organic compound involves dissolving the impure substance in a suitable solvent or a mixture of solvents, filtering the hot solution

and allowing the hot solution to cool. This causes the dissolved substance to crystallise out and separates the crystals from supernatant solution and dries the resulting crystals. The examples stated in the Application illustrate the preparation of various forms of Lopinavir crystals, which follow similar steps as mentioned above, that would be obvious to someone skilled in the art. Moreover, the Application is completely silent on what technical problem is overcome by the various crystalline forms of Lopinavir. The Application fails to demonstrate any unexpected effect of crystalline forms of Lopinavir over the known amorphous form of Lopinavir as disclosed in US Patent No. 5914332.

Claims 1-23 of the invention are not patentable under the Section 25(h) and Section 8 of the Act

17. Section 8(1)(a) and (b) make it an obligation on the Applicant to keep the Controller informed of an application which is being prosecuted in another country and which is considered to be the same as the invention applied for in India. This obligation requires the Applicant to provide, within a prescribed period as the Controller may allow, a statement setting out detailed particulars of the application being prosecuted in another country and an undertaking to keep the controller informed of the same up to the date of grant of the said patent in India. Section 8 is read into s25(1)(h) as a ground of opposition to the grant of a patent. Based on the above, the Opponents question whether the Applicant has provided this Patent Office with the information and particulars of the equivalent foreign applications that the Applicant is currently prosecuting.

18. In light of such obligations on the Applicant, the Opponents are aware that the Applicant has applied to patent the same invention claimed in the Application, under European Patent Application No. 01924250.2, titled "Crystalline Pharmaceutical", published on 2 January 2003. The Opponents understand that the European Patent Application No. 01924250.2 has to date not been granted. Moreover, it has come to the notice of the Opponents that the European Patents Office's examination reports for the said application have observed that claims 1-23 of the Application are obvious. The Opponents seriously doubt whether the Applicant has informed this Patent Office of the status of its European Patent Application and the pending observation process. As a result, the Applicant's failure to do so is a strict ground to refuse the Application in its entirety.

19. In any event, the Opponents ask to be kept informed throughout these proceedings as to whether the Applicant has provided this Patent Office with the required details of matters relating to the corresponding application in European Patent Office. The Opponents believe such matters are relevant to proceedings here, albeit, of course, the laws are different. Moreover, the Opponents also request this Patent Office exercise its discretion under Section 8(2) and require the Applicant to furnish details of the processing of the abovementioned European application.

In light of the above, the Opponents hereby 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. Claims 1-23 of the present Application fail for lack of novelty; and

c. Claims 1-23 in the present Application fail for lack of inventive step.

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

Dated 4th August 2006

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

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For and behalf of the Delhi Network of Positive People (DNP+)

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For and behalf of the Network of Maharastra by People Living with HIV/AIDS (NMP+)

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

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To:
The Controller of Patents,
The Patent Office, Mumbai