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

The Patent Controller,
Delhi

RE: Patent Application 727/DEL/1997A, "Pharmaceutical Formulations", filed 21 March 1997 by Glaxo Group Limited

STATEMENT OF OPPOSITION

1. The Uttar Pradesh Network of Positive People ("UPNP+"), a community-based, non-profit organisation, Society Registration Number 3/173, registered under the Societies Registration Act of 1889, and the Indian Network of Positive People ("INP+"), a community-based, non-profit organisation, registered as a society under the Tamil Nadu Societies Registration Act in May 1997, (collectively, 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, against the grant of patent application, titled: "Pharmaceutical Formulations," made by Glaxo Group Limited (the "Applicant"), bearing Indian patent application No. 727/DEL/1997A filed on 21 March 1997 (the "Application"). This representation is proper under section 25(1) of the Act as the application has been published but a patent has not been granted.

2. INP+ is a national community-based organization representing the needs of People Living with HIV/AIDS ("PLHAs"). INP+ is the national level organization and has under its umbrella many organizations at the State level. UPNP+ is the state of Uttar Pradesh's state-level member network of INP+. The essence of both INP+ and UPNP+ is to provide a voice 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. They are vitally concerned about the availability of antiretroviral drugs to the PLHAs of 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. The Opponents therefore have a direct interest in whether the Application is granted patent.

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

4. The Indian Patents (Amendment) Act, 2005 was passed to bring India into compliance with its obligations under TRIPS, and introduced a 20-year product patent regime. However, India is also a signatory to the Doha Declaration on the TRIPS Agreement and Public Health (the Doha Declaration), which states

> "… we affirm that the [TRIPS] Agreement can and should be interpreted and implemented in a manner supportive of the WTO members' right to protect public health and, ***in particular, to promote access to medicines for all.***" (emphasis added)

5. The Opponents respectfully submit that the obligation to promote access to medicines for all must be upheld and that the Patents Act must be interpreted to give effect to this aim. The Doha Declaration should be the underlying value system that informs all patent examinations.

6. Furthermore, the Opponents submit that the Doha Declaration has been incorporated into the Patents Act by Parliament through provisions that protect public health. Patents are given to inventions in exchange for advances in science and technology. Where drug companies are granted patents for only minor improvements of existing drugs, they are at liberty to set the prices of the drugs, and often fix prices well beyond the means of the average person in the developing world and in India. Granting patents for such frivolous applications are thus injurious to both scientific advance and to public health. Parliament has sought to deny patent protection to such frivolous claims and has rejected the

practice of "evergreening". Perhaps the most important provision in this regard is section 3(d), which prohibits patents for "a new form of a known substance which does not result in the enhancement of the known efficacy of that substance" or for the mere discovery of a "new use of a known substance".

7. The present Application comprises merely of a combination of known substances – a protease inhibitor with tocopherol, or Vitamin E – to achieve a known result. In a further formulation, known solvents are added to make the combination more flowable and cheaper to manufacture. The Application relates precisely to the type of minor improvement that Parliament sought to exclude from patent protection, through section 3(d) of the Patents Act. We respectfully submit that the Application for patent should be rejected.

DESCRIPTION OF CLAIMS AND SCOPE OF THE INVENTION

8. The Opponents have studied the specification and the claims made by the Applicant and strongly believe that the Application is not eligible for patent protection. We oppose on the following grounds:
   a) 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 of the claim elsewhere in any other document;
   b) 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;
   c) 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) and 3(e);
   d) Section 25(1)(g) – that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

9. Accordingly, under section 25(1) of the Act and Rule 55(1) of the Rules, the Opponents seek to oppose this Application for patent for the reasons set out below.

10. The Application relates to the combination of a known protease inhibitor with a known emulsifier and known solvents. Specifically, the alleged invention relates to adding to the known protease inhibitors, water-soluble tocopherols, most particularly Vitamin E-TPGS, to increase drug solubility, and non-aqueous solvents, specifically polyethylene glycol, propylene glycol or polyvinyl pyrrolidone, to increase flowability. The Applicant's claims can be summarized as follows:

    a. Claim 1 relates to a pharmaceutical composition comprising an HIV protease inhibitor and a water soluble tocopherol.

    b. Claims 2 and 3 are dependent on Claim 1 and specify the ratio and amounts of the compositions that should be used.

    c. Claim 4 relates to a pharmaceutical composition comprising a protease inhibitor, a water-soluble tocopherol and non-aqueous solvents.

    d. Claims 5 and 8 are dependent on Claim 4 and relate to the amount of water soluble tocopherol and the most appropriate solvents.

    e. Claims 6 and 7 are dependent on Claims 1 and 4 and relate to the range of ingredients to be used and the use specifically of Vitamin E-TPGS.

    f. Claim 9 relates to a pharmaceutical composition where an HIV protease inhibitor is combined with Vitamin E-TPGS, polyethylene glycol and propylene glycol.

g. Claims 10 and 11 are dependent on Claims 1, 4 or 9 relating to the use of amprenavir in any of the formulations, and to a capsule form of any composition.

h. Claim 12 relates to the method for dissolving an HIV protease inhibitor in a water soluble tocopherol.

GROUNDS

11. It is clear that all the claims relate directly or indirectly to dissolving a protease inhibitor in a water soluble tocopherol, sometimes with the addition of a non-aqueous solvent. However, neither of these formulations is patentable under the Act because:

    a. The alleged invention is known and is not novel;
    b. The alleged invention is obvious and does not involve an inventive step;
    c. The alleged invention is merely a new use of a known substance;
    d. The alleged invention is a new form of a known substance that does not result in an enhancement of efficacy;
    e. The alleged invention is a mere admixture under section 3(e);
    f. The specifications do not adequately support the claims as required by section 10(5).

Each of these separate and independent grounds for denying a patent - which are without prejudice to one another - is discussed in detail below.

a. The alleged invention is known and is not novel

12. An invention is defined under section 2(j) as a ***new*** product or process involving an inventive step and capable of industrial application (emphasis added). Section 25(1)(b) provides the basis for denying an application if the invention has been published before the priority date of the claim, in India or elsewhere, in any other

document. Thus, if a publication published prior to the present Application discloses the claimed invention, then the Application lacks novelty and must be rejected.

13. In assessing novelty, it has been held that a person reasonably skilled in the art would have allowed some room for trial and error when practicing the prior art, and that the need for some experimentation from the teaching of the prior art should not defeat novelty. It is respectfully submitted that the Patent Office should follow this interpretive approach in assessing the meaning and scope of prior art and prior publication.

14. The Applicant seeks to claim the addition of water soluble tocopherols to any of the class of protease inhibitors as a new invention. To do so, it characterizes protease inhibitors as a unique category of compounds about which little is known or taught. In fact, protease inhibitors belong to a broader class of lipophilic, insoluble compounds with low bioavailability (see Application, p. 3; lines 3-5; Norbeck et al "HIV Protease Inhibitors" *Annu. Rep. Med. Chem.* (1991) Vol. 26, 141-150 at page 148, second paragraph, attached as Exhibit A; Debouck et al "Human Immunodeficiency Virus Protease Inhibitors: A Target for AIDS Therapy" *Drug Dev. Res*. (1990) Vol. 21, 1-17 at page 6, second paragraph, attached as Exhibit B). Patents published before the priority date of this Application proposed enhanced drug delivery systems for insoluble, lipophilic active agents by using Vitamin E-TPGS as an excipient.

15. Patent WO9531217 "Tocopherol Compositions for Delivery of Biologically Active Agents" (published 23 November 1995, attached as Exhibit C), which the Applicant cites, claims the use of tocopherol as a solvent and emulsifier of insoluble biologically active agents, especially for the manufacture of pharmaceutical compositions. Claim 3 claims: "A composition for the delivery of a substantially insoluble or sparingly soluble biologically active agent, comprising said agent dissolved in tocopherol or a derivative thereof." Furthermore, Claim

14 claims the composition of claim 3, "further comprising one or more additional components selected from solvents, surfactants, stabilizers, bioadhesive polymers, preservatives and odour- or taste-masking agents." Although the specification describes the invention as particularly suitable for transmucosal administration, the description mentions that the formulation may also be used to prepare composition in tablet, capsule or solution form (see page 6 of the Description). Further, the claims, which under section 10 of the Patents Act define the scope of the invention, claim the general formulation. The invention does not claim the use of lipophilic phase in the claims.

16. The Opponents humbly submit that these claims exactly cover the Applicant's use of both a water-based tocopherol and of non-aqueous solvents to enhance the delivery of insoluble protease inhibitors. The earlier patent renders the alleged invention known under the Patents Act.

17. Further, Patent WO9525504 "Emulsified Drug Delivery Systems" (published 28 September 1995, attached as Exhibit D) discloses "a pharmaceutical preparation comprising a stable emulsion of a pharmaceutical agent incorporated into a hydrophobic emulsion of a long chain carboxylic acid, long chain carboxylic acid ester, long chain carboxylic acid alcohol and mixtures thereof in a dosage form suitable for oral delivery." The claims specifically mention Vitamin E-TPGS as a suitable long chain carboxylic acid ester. The invention does not rely on a lipophilic phase. Since protease inhibitors are pharmaceutical preparations that are substantially insoluble, their combination with Vitamin E-TPGS and other water-soluble tocopherol derivatives is disclosed by Patent WO9525504. On the basis of the above, the alleged invention is disclosed in an earlier patent and Claims 1-11 should be rejected under section 25(1)(b)(ii).

18. Furthermore, the description and Claim 10 of the Application cite amprenavir as the preferred protease inhibitor for working the alleged invention. Amprenavir is disclosed in Patent WO9405639 "Sulfonamide Inhibitors of HIV-Aspartyl"

(published 17 March 1994, excerpts attached as Exhibit E. The Opponent craves leave to produce the full document, as and when required). The Applicant itself relies on WO9405639 (see Application, p.2, line 8). Claim 15 of Patent WO9405639 claims "a pharmaceutical composition effective against viral infection comprising a pharmaceutically effective amount of [amprenavir] and a pharmaceutically acceptable carrier, adjuvant or vehicle". Since water-based tocopherols and non-aqueous solvents are both known in the art as acceptable carriers, their use is disclosed. The Opponents respectfully submit that this disclosure is sufficient to render the use of water-based tocopherols and solvents with amprenavir known, and on this basis Claim 10 should be rejected.

b. The invention is obvious and does not involve an inventive step

19. In the alternative and without prejudice to the grounds raised above, under section 2(j), an invention must involve an inventive step. Section 2(ja) provides that an inventive step means a "feature of an invention that involves a technical advance compared to existing knowledge and that makes the invention not obvious to a person skilled in the art". If an alleged invention was obvious to one skilled in the art, given all the prior art available at the time, then there is no inventive step and no patent may be granted.

20. The Applicant admits that a known problem in administering protease inhibitors is their low bioavailability. The Applicant further admits that the protease inhibitors that it seeks to use, and specifically amprenavir, were known (see Application, p. 1, lines 14-31 and p.2, lines 8-10), and that the class of water-soluble tocopherols, particularly Vitamin E-TPGS, were known (see Application, p.4, lines 4-14). It seeks to claim that combining these two known products, protease inhibitors and water soluble tocopherols, provides a solution to the problem by producing a more bioavailable form. However, it was already known in the field that the addition of water-soluble tocopherols, and particularly Vitamin E-TPGS, improves the bioavailability of insoluble compounds.

21. The above patents (Patent WO9531217 "Tocopherol Compositions for Delivery of Biologically Active Agents", published 23 November 1995 and Patent WO9525504 "Emulsified Drug Delivery Systems", published 28 September 1995) teach that insoluble compounds can be rendered more bioavailable by adding tocopherols and their derivatives. It is humbly submitted that it would have been obvious to one skilled in the art, given the teachings in those patents, to combine water soluble tocopherols with protease inhibitors to increase their bioavailability.

22. Other texts available at the time also describe how water soluble vitamin E – and particularly Vitamin E-TPGS – can be used to increase absorption of fat soluble substances and enhance drug delivery (see Sokol et al "Improvement of cyclosporine absorption in children after liver transplantation by means of water-soluble vitamin E" *The Lancet* Vol 338 (1991) 212-4, at 214. left hand column, second paragraph; attached as Exhibit F; Argao et al "d-Alpha-tocopherol polyethylene glycol-1000 succinate enhances the absorption of vitamin D in chronic cholestatic liver disease of infancy and childhood" *Pediatric Research* Vol 31 (1992) 146-150, at page 149, right hand column, second paragraph; attached as Exhibit G). Given that the low solubility and consequent low bioavailability of protease inhibitors was known, it would have been obvious to one skilled in the art to try the combination of water-soluble tocopherols and protease inhibitors to increase bioavailability.

23. On the basis of the above, the Opponents respectfully submit that Claims 1-3 relate to a product that was obvious given the state of the prior art, and should be rejected under section 25(1)(e) of the Patents Act.

24. Similarly, the addition of solvents was known and had been used *for years* to make solutions suitable for pharmaceutical compositions. The addition of a solvent to the mixture of an insoluble compound and tocopherol was disclosed in Patent WO9531217 and has been discussed above.

25. It was also known in particular that propylene glycol, polyethylene glycol and polyvinyl pyrrolidone were good solvents for hydrophilic, insoluble drugs, and can themselves enhance bioavailability (see, for example, Yonish-Rouach et al "A method for preparing biologically active aqueous cyclosporin A solutions avoiding the use of detergents or organic solvents" *Journal of Immunology Methods* Vol. 135 (Dec, 1990), 147-53 at p.152, left hand column, second paragraph; attached as Exhibit H; Sugahara et al "Absorption of new HIV-1 protease inhibitor, KNI-272, after intraduodenal and intragastric administrations to rats: effect of solvent" *Biopharmaceutics and Drug Disposition* Vol. 16 (May, 1995), 269-77, abstract attached as Exhibit I. The full text of this article will be provided at hearing). The addition of non-aqueous solvents, and particularly of propylene glycol, polyethylene glycol or polyvinyl pyrrolidone, would have been obvious to one skilled in the art. On this basis, and under section 25(1)(e), the Opponents respectfully submit that Claims 4, 5, 6, and 9 must be rejected on the basis that they are obvious.

26. It should be noted at this point that although the Applicant claims all water-soluble tocopherol derivatives for dissolving protease inhibitors, the Applicant's description only discloses the effective use of Vitamin E-TPGS. The invalidity of this approach will be discussed further below. At this point, however, the Opponents humbly submit that the Applicant has failed to show that any other water-soluble tocopherol is effective, and that the invention should be confined to the use of Vitamin E-TPGS with a protease inhibitor. It is submitted that all generalized claims – that is, Claims 1, 2, 3, 4, 5 and 6 – should, in any case, be rejected.

27. The Opponents humbly submit that the obviousness of dissolving a protease inhibitor in water soluble tocopherol, specifically Vitamin E-TPGS, and of the use of a non-aqueous solvent, read cumulatively, require Claims 1-11 to be rejected.

c. <u>The invention is merely a new use of a known substance</u>

28. Section 3(d) of the Patents Act states that the new use of a known substance is not an invention. In the alternative and without prejudice to the grounds raised above, Claims 1-11 of the present Application relate, at most, to the new use of a known substance, water-soluble tocopherol, to dissolve protease inhibitors.

29. Vitamin E-TPGS was first developed and patented in the 1950s (see Patent US2680749 "Water soluble tocopherol derivatives", 8 June 1954, attached as <u>Exhibit J</u>). Its use as an excipient has been known for decades. By extension, the class of water-soluble tocopherol derivatives, of which Vitamin E-TPGS is a member, was also in use. Using Vitamin E-TPGS – and by extension, other water-based tocopherols – to dissolve a known substance and thereby increase drug delivery is, at best, a new use of Vitamin E-TPGS and other water soluble vitamin E derivatives.

30. Similarly, non-aqueous solvents, including propylene glycol, polyethylene glycol or polyvinyl pyrrolidone, have long been in use in other products. Using these solvents with known protease inhibitors and water soluble tocohperols for the purpose of drug formulation is merely a new use of these known substances and is not patentable under section 3(d).

31. The Opponents respectfully submit that since both primary compositions claimed – the addition of a water-soluble tocopherol derivative to a protease inhibitor, and the addition of non-aqueous solvents to a water based tocopherol derivative and a protease inhibitor – merely disclose new uses of known substances, Claims 1-11 of the Application should be rejected under section 25(1)(f).

d. <u>The invention is a new form of a known substance that does not result in the enhancement of known efficacy</u>

32. Under section 3(d) of the Patents Act, a new form of a known substance is not an invention unless it enhances the efficacy of the substance. In the alternative and without prejudice to the grounds raised above, the present alleged invention relates only to a new form of a known substance, and is not eligible for patent.

33. It is respectfully submitted that combining a known excipient or emulsifier and a known solvent with a known protease inhibitor does not change the nature of the compound. The active ingredient remains, in all cases, the known protease inhibitor. Thus, adding a water soluble tocopherol or any non-aqueous solvent merely gives rise to a new form of a known substance, but does not change the substance itself.

34. The Application makes no direct claims about the efficacy of the new form as against other protease inhibitors. It only states that dissolving amprenavir in Vitamin E-TPGS leads to a more bioavailable form of amprenavir (see Application, p. 3, lines 33-4; p.4 lines 1-2). However, the Indian Patent Office has found that increased bioavailability is not an enhancement of efficacy under section 3(d) (*Novartis v. AG Cancer Patients A.J. Association, India* (Application No. 1602/MAS/98, decision of 25 January 2006), attached as Exhibit K). This is because bioavailability relates to the amount of drug that is absorbed after administration. In contrast, efficacy is a narrow concept relating only to how successfully a drug can *treat* a disease. Drug efficacy can only be determined by clinical trials. The burden lies on the Applicant to provide evidence from clinical trials to establish an enhancement of efficacy of this form of amprenavir as against earlier forms of amprenavir. The Applicant has not met this burden.

35. Even if bioavailability were to be equated with efficacy, the Applicant has not established a sufficient increase in bioavailability to show that the new form differs "significantly . . . with regard to efficacy", as required by section 3(d). An increase in bioavailability must be demonstrated by comparing the parent application with the present Application. The parent application, Patent

WO9405639 "Sulfonamide Inhibitors of HIV-Aspartyl" (cited above, Exhibit E), discloses both an oral and intravenous form of amprenavir (see WO9405639 at p.32, paragraph 3-4). The current Application must therefore show a significant enhancement in efficacy over both forms.

36. The current Application compares the solubility of the previous formulation with the solubility of the alleged invention, and reaches the conclusion that an oral formulation of the former will be less bioavailable than the latter. However, no figures relating to this increase in bioavailability between the two oral formulations are provided, and the Applicant has therefore not met its burden under section 3(d).

37. Furthermore, the Application does not make any comparison between bioavailability of the parent application's intravenous form and the present oral form. It seems highly likely the intravenous form is more bioavailable than the oral form. Thus, an increase in bioavailability over the parent application cannot be established and no enhancement of efficacy is shown.

38. The other benefit that the Application claims is derived from dissolving protease inhibitors in water based tocopherol is the advantage of not relying on a lipophilic phase. According to the Applicant, the absence of the lipophilic phase results in smaller, cheaper and easier to manufacture forms (see Application, p.5, lines 17-20). These factors are unrelated to the efficacy of the drug. Whether a pill is small or cheap and easy to manufacture does not affect the drug's ability to treat and cure. These factors merely make the manufacture of the drug more convenient for the Applicant itself.

39. Similarly, the addition of solvents improves the physical properties of the formulation, allowing mass formulation (see Application, p. 6, lines 14-19), increases bioavailability, and makes the mixture more flowable. Again, none of

these improvements relate to the efficacy of the drug, and do not constitute an enhancement of efficacy.

40. It is respectfully submitted that no enhancement of efficacy is claimed or established and Claims 1-11 – all of which are merely new forms of known substances – should be rejected under section 25(1)(f) of the Patents Act.

e. <u>The invention is a mere admixture of a protease inhibitor, water soluble tocopherol and solvents which results only in the aggregation of their properties</u>

41. In the alternative and without prejudice to the grounds raised above, under section 3(e) of the Patents Act, an alleged invention is not eligible for patent if it amounts to a "mere admixture resulting only in the aggregation of the properties of the components thereof."

42. As outlined above, combining a water soluble tocopherol derivative with a protease inhibitor merely combines the medicinal properties of the protease inhibitors with the emulsifying properties of the tocopherol. The effect of using the two together is that the tocopherol lends its properties to the protease inhibitor; this is a mere aggregation of properties.

43. Similarly, adding solvents to the tocopherol derivative/protease inhibitor combination creates a solution. The usual properties of solvents are exploited, but again admixture only leads to an aggregation of properties.

44. The Opponents respectfully submit that combining a protease inhibitor and a water soluble tocopherol derivative, with or without further adding a solvent, amounts to mere admixture that aggregates the properties of each component. On this basis, Claims 1-11 of the Application should be rejected under section 24(1)(f).

f. <u>The specification does not adequately support the claims</u>

45. In the alternative and without prejudice to the grounds raised above, section 10(5) of the Patents Act states:

> "The claim or claims of a complete specification shall relate to a single invention . . . and shall be fairly based on the matter disclosed in the specification."

If the alleged invention claimed in the claims does not match the alleged invention described in the specification, then the requirements of section 10(5) are not met, and the Application may be rejected under section 25(1)(g).

46. The Applicants description states that they found that Vitamin E-TPGS combined with amprenavir gave rise to a more bioavailable form (Application, p. 3; lines 33-4; p.4 lines 1-2). The examples then continue to outline how vitamin E-TPGS can be used. No mention is made of any other water soluble tocopherol derivatives, either by name or patent number. However, the use of any water soluble tocopherol derivative is claimed. In contradistinction, the Applicant claims all protease inhibitors, but cites possible candidates by patent number.

47. The Opponents respectfully submit that the Applicant has not met its burden in establishing that other forms of water soluble tocopherol derivatives can be worked in the invention. The description in the specification is insufficient to claim the entire class of water soluble tocopherol derivates. The claims are therefore overbroad where they claim all water soluble tocopherol derivatives. Claims 1 to 6 of the Application should accordingly be rejected under section 25(1)(g).

<u>CONCLUSION</u>

48. Given all of the foregoing, the Opponents humbly request the Patent Office to reject the Application on all or any of the following grounds, which are without prejudice to one another:

    a. The alleged invention is known and is not novel;

    b. The alleged invention is obvious and does not involve an inventive step;

    c. The alleged invention is merely a new use of a known substance;

    d. The alleged invention is a new form of a known substance that does not result in an enhancement of efficacy;

    e. The alleged invention is a mere admixture under section 3(e);

    f. The specifications do not adequately support the claims as required by section 10(5).

    Any of these grounds is sufficient to establish that the Application does not disclose an invention and cannot give rise to a patent.

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

Respectfully submitted,

On Behalf of the Uttar Pradesh Network of Positive People,

_____
_____

Naresh Chandra Yadev Date

On Behalf of the Indian Network of Positive People,

_____
_____

K.K. Abraham Date