

THE PATENT ACT 1970

IN THE MATTER OF:

Statement under section 25(1) of the Patent Act, 1970 as amended by the Patents (Amendment) Act 2005 (“the Act”) and Rule 55 of The Patent Rules 2003 as amended by the Patents (Amendment) Rules 2006 (“the Rules”) by Abbott Laboratories, USA.....**Applicant**

And

IN THE MATTER OF:

Opposition filed against Indian patent application no. **339/MUMNP/2006** on 9th October 2007, by the Initiative for Medicines, Access and Knowledge (I-MAK).....**Opponent**

STATEMENT OF THE APPLICANT

We, **Abbott laboratories, USA, a corporation organized and existing under the laws of Illinois, having its place of business at 100 Abbott Park Road, Abbott Park, Illinois 60064-6050, U.S.A.**, the Applicant herein states and submits paragraph wise reply to the alleged written statement submitted by the opponents, the *Initiative for Medicines, Access and Knowledge (I-MAK)* in respect of the pre-grant opposition filed in respect of the above identified patent application no. 339/MUMNP/2006 (herein after referred to as “present invention”).

A. It is submitted that the Applicant is a global, broad-based health care company devoted to discovering new medicines, new technologies and new ways to manage health. Applicant’s products span the continuum of care, from nutritional products and laboratory diagnostics through medical devices and pharmaceutical therapies. Applicant’s comprehensive line of products encircles life itself – addressing important health needs from infancy to the golden years. Applicant’s diverse family of pharmaceutical, medical, and nutritional products includes a broad range of specialized medicines; medical diagnostic instruments and tests; minimally invasive surgical devices; a spectrum of nutritional supplements for infants, children and adults; and products for veterinary care.

- 9 JAN 2008

PRELIMINARY OBJECTIONS:

B. Under Rule 55(1) of the Rules, the Opponent is required to file evidence in support of opposition. In the present proceedings, the opponent has not filed any evidence to support their opposition and hence have failed in providing any technical or expert evidence to support their allegations and statements in the written statement. On this very ground of want of substantial evidence to prove the allegations, the pre-grant opposition should be dismissed

REPLY ON MERITS

- 1 This paragraph of the written statement needs no reply. We are unaware of the constitution of The Initiative for Medicines, Access and Knowledge (I-MAK). However, the opponent has misused the provisions of section 25(1) of the Indian Patents Act and has used it as a tool to defeat, stall and delay the grant of patents on patent applications by filing **frivolous** pre-grant oppositions in the guise of public interest.
- 2 The contents of this paragraph are admitted to the extent that application no. 339/MUMNP/2006 filed on 24th March 2006 stems from the International Application number PCT/US2004/027401 filed on 23rd August 2004, claiming a priority date of 28th August 2003. This application was notified in Part II of the official journal of the Patent Office on 29th June 2007.
- 3 This paragraph needs no reply.
- 4- 5: (i) In this regard, it is respectfully submitted that the opponents have a history since their inception to stall the grant of patents for all pharmaceutical patent applications globally directly or indirectly related to particularly HIV treatment. The opponent has in their written statement attempted to justify the use of Section 25(1) as an effective tool to filter frivolous inventions.

(ii) In fact, the opponents seem to have taken to the role of Patent Office in attempting to do such acts. It is submitted that the opponent seem to justify their deeds and acts in guise of social cause and public health and have failed to realize that they are in fact by their actions and conduct working against the interest of research and development at large and also against the public by denying them access to newer medicines.

(iii) From the written statement, it appears that the opponent is against the grant of patents to the best and newest pharmaceutical treatments, which according to him will make their availability too expensive or limited. **This is not a ground provided under Section 25(1) of the Indian patents Act.**

Moreover, in low- and lower middle-income countries, the applicant's, Abbott's Lopinavir/ritonavir tablets are among the most affordable of protease inhibitors that are recommended in the World Health Organization, U.S. Department of Health and Human Services, the British HIV Association, and the International AIDS Society-USA guidelines. In many Africa and least developed countries, Abbott's Lopinavir/ritonavir tablets cost less than what the lowest priced generics cost. The applicant, Abbott will continue to focus its efforts on making its HIV medicines available and affordable in the areas of greatest need.

(iv) Further, the opponent has failed to appreciate that the **Patent Office is not the appropriate forum** to address the issues of health care, support, access to treatment.

(v) The opponent has failed to appreciate that drug pricing and drug availability do not come within the ambit of Patents. Inherently, patents are granted to provide exclusivity to the innovator which the opponent has not understood. The issue of drug pricing and availability ought to be addressed by a separate legislative and /or administrative actions/order.

(vi) The opponent is unnecessarily trying to put pressure upon the Patent Office with frivolous, unsubstantiated and unjustified oppositions and therefore the opponent's conduct is questionable.

(vii) Further, the opponent has also failed to appreciate that in order to safe guard public health interest of the citizens of India, the Government has taken several measures while drafting the patent legislation to prevent patent abuse and dealing with emergency situations (like the grant of compulsory license under the Indian Patents Act) and other legislations and administrative order (such as the DPCO).

Moreover, the opponent has failed to recognize and appreciate the legislative intent of the Patents Act which is carefully designed so as to ensure that there is an appropriate balance viz a viz there is no abuse of patent rights and that patents are used to ensure technological transfer to the benefit of public and society at large.

In this regard, we would like to bring the attention of the Hon'ble Controller that there are several inbuilt mechanisms within the Indian Patents Act which ensures an appropriate balance between the rights conferred upon the patent holder and public at large such as provisions relating to grant of a compulsory license as in situations of national emergency, extreme emergency or public non-commercial use which may arise or is required, as the case may be, including public health crises, relating to Acquired Immuno Deficiency Syndrome, Human Immuno Deficiency Virus, Tuberculosis, Malaria or other epidemics.

Having said this, the written statement of the opponent in paragraph 5 seem to suggest that a patent ought not to be granted to any anti retro-viral drug as in its opinion, the grant of patent will “impede” others from the development of anti-HIV drugs in particular, Lopinavir/Ritonavir at affordable prices.

Such statements of the opponent are a clear reflection of their objectives of **not allowing the grant of patents** as according to them the grant of patents has a direct impact on accessibility, affordability and development

It is therefore submitted that the opponent has no basis or grounds to suggest that the grant of a patent to the present invention will contribute to preventing HIV patients from accessing this particular treatment at a cost they can afford.

As submitted above, the applicant besides being conscious of the need of anti retroviral drugs to HIV patients has already taken steps in order to ensure that the said drugs are available at affordable prices.

viii) It is further submitted that opponent appears to dictate the Patent Office with regard to assessment of the applicant’s patent application No. 339/Mumnp/2006 for the grant of patent under the scheme of the Indian Patents Act and Rules and through out its written statement seems to misguide the Patent office.

It is therefore submitted that the pre-grant opposition of the opponents be out rightly dismissed especially in view of the malafide intentions of the opponent.

6-7. These paragraphs need no reply

8. It is submitted that the opponent has simply summarized the pending claims of the application. However, in view of the fact that the aforesaid patent application is still pending prosecution, the applicant wishes to amend the claims of the present application to as follows:

1. A pharmaceutical composition which comprises a solid dispersion of at least one HIV protease inhibitor in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-(N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir), and each of said at least one pharmaceutically acceptable water-soluble polymer has a Tg of at least about 50 °C, and said composition comprises from about 50 to about 85

% by weight of the total composition of said at least one pharmaceutically acceptable water-soluble polymer.

2. The pharmaceutical composition of claim 1, wherein said solid dispersion is a glassy or solid solution.

3. The pharmaceutical composition of claim 1, wherein said surfactant has an HLB value of from about 4 to about 10.

4. The pharmaceutical composition of claim 1, wherein said at least one pharmaceutically acceptable surfactant is a combination of at least one pharmaceutically acceptable surfactant having an HLB value of from about 4 to about 10 and at least one further pharmaceutically acceptable surfactant.

5. The pharmaceutical composition of claim 1, wherein said surfactant is a sorbitan fatty acid ester.

6. The pharmaceutical composition of claim 1 which comprises, relative to the weight of the solid dosage form, from about 5 to about 30 % by weight of said at least one HIV protease inhibitor, from about 2 to about 20 % by weight of said at least one pharmaceutically acceptable surfactant, and from about 0 to about 15 % by weight of additives.

7. The pharmaceutical composition of claim 1, wherein said at least one HIV protease inhibitor further includes (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane (lopinavir).

8. The pharmaceutical composition of claim 1, wherein each of said at least one pharmaceutically acceptable water-soluble polymer has a Tg of from about 80 to about 180 °C.

9. The pharmaceutical composition of claim 1, wherein said water-soluble polymer is a homopolymer or copolymer of N-vinyl pyrrolidone.

10. The pharmaceutical composition of claim 1, wherein said water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate.

11. The pharmaceutical composition of claim 1 containing at least one additive selected from flow regulators, disintegrants, bulking agents and lubricants.

12. The pharmaceutical composition of claim 1 which comprises, relative to the weight of the composition, from about 5 to about 30 % by weight of said at least one HIV protease inhibitor, from about 2 to about 20 % by weight of said surfactant, and from about 0 to about 15 % by weight of additives.

13. The pharmaceutical composition of claim 1, wherein each of said at least one pharmaceutically acceptable water-soluble polymer is selected from the group consisting of homopolymer of N-vinyl lactam, copolymers of N-vinyl lactam, cellulose ester, cellulose ether, polyalkylene oxide, polyacrylate, polymethacrylate, polyacrylamide, polyvinyl alcohol, vinyl acetate polymer, oligosaccharide, and polysaccharide; and wherein said surfactant is selected from the group consisting of polyoxyethylene alkyl ether, polyoxyethylene alkylaryl ether, polyethylene glycol fatty acid ester, alkylene glycol fatty acid mono ester, sucrose fatty acid ester, and sorbitan fatty acid mono ester.

14. The pharmaceutical composition of claim 1, wherein each of said at least one pharmaceutically acceptable water-soluble polymer is selected from the group consisting of homopolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone, copolymer of N-vinyl pyrrolidone and vinyl acetate, copolymer of N-vinyl pyrrolidone and vinyl propionate, polyvinylpyrrolidone, methylcellulose, ethylcellulose, hydroxyalkylcelluloses, hydroxypropylcellulose, hydroxyalkylalkylcellulose, hydroxypropylmethylcellulose, cellulose phthalate, cellulose succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate, hydroxypropylmethylcellulose acetate succinate, polyethylene oxide, polypropylene oxide, copolymer of ethylene oxide and propylene oxide, methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, butyl methacrylate/2-dimethylaminoethyl methacrylate copolymer, poly(hydroxyalkyl acrylate), poly(hydroxyalkyl methacrylate), copolymer of vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl acetate, carrageenan, galactomannan, and xanthan gum, and wherein said surfactant is selected from the group consisting of polyoxyethylene (3) lauryl ether, polyoxyethylene (5) cetyl ether, polyoxyethylene (2) stearyl ether, polyoxyethylene (5) stearyl ether, polyoxyethylene (2) nonylphenyl ether, polyoxyethylene (3) nonylphenyl ether, polyoxyethylene (4) nonylphenyl ether, polyoxyethylene (3) octylphenyl ether, PEG-200 monolaurate, PEG-200 dilaurate, PEG-300 dilaurate, PEG-400 dilaurate, PEG-300 distearate, PEG-300 dioleate, propylene glycol monolaurate, sucrose monostearate, sucrose distearate,

sucrose monolaurate, sucrose dilaurate, sorbitan mono laurate, sorbitan monooleate, sorbitan monopalmitate, and sorbitan stearate.

15. The pharmaceutical composition of claim 13, wherein said at least one pharmaceutically acceptable water-soluble polymer is a homopolymer or copolymer of N-vinyl pyrrolidone, and said surfactant is a sorbitan fatty acid ester.

16. The pharmaceutical composition of claim 14, wherein said at least one pharmaceutically acceptable water-soluble polymer is copovidone, and said surfactant is sorbitan monopalmitate.

17. The pharmaceutical composition of claim 13, wherein said at least one pharmaceutically acceptable water-soluble polymer is a homopolymer or copolymer of N-vinyl pyrrolidone, and said surfactant is a sorbitan fatty acid ester, and wherein said at least one HIV protease inhibitor is present in an amount of from about 5 to about 30 % by weight of the composition, and said surfactant is present in an amount of from about 2 % to about 20 % by weight of the composition.

18. The pharmaceutical composition of claim 17, wherein said solid dispersion is a glassy or solid solution.

19. The pharmaceutical composition of claim 17, wherein said at least one pharmaceutically acceptable water-soluble polymer is a copolymer of N-vinyl pyrrolidone and vinyl acetate.

20. The pharmaceutical composition of claim 17, wherein said at least one pharmaceutically acceptable water-soluble polymer is copovidone, and said surfactant is sorbitan monopalmitate.

21. The pharmaceutical composition of claim 17, wherein said at least one HIV protease inhibitor further comprises lopinavir.

22. The pharmaceutical composition of claim 20, wherein said at least one HIV protease inhibitor further comprises lopinavir, and said solid dispersion is a glassy or solid solution.

23. A method of preparing a pharmaceutical composition of claim 1, comprising:

preparing a homogeneous melt comprising said at least one HIV protease inhibitor, said at least one pharmaceutically acceptable water-soluble polymer and said at least one pharmaceutically acceptable surfactant; and

allowing the melt to solidify to obtain a solid dispersion product.

24 The method of claim 23 additionally comprising grinding said solid dispersion product and compressing said solid dispersion product into a tablet.

25 A pharmaceutical composition comprising a solid dispersion of at least one HIV protease inhibitor in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant, wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-(N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) as and when prepared by a process as claimed in claim 23.

9. The opponent has relied on three grounds and to substantiate said grounds has submitted exhibits 1-15. The grounds taken by the opponent are as follows:
- a. not an invention [25(1)(f)],
 - b. obviousness [25(1)(e)]
 - c. Information under section 8, [25(1)(h)].

Before addressing the aforementioned grounds of opposition the Applicant wishes to draw the kind attention of the Learned Controller to the fact that the first examination report dated October 11, 2006 has been issued in respect of the present patent application and the applicant has sufficient time to deal with the objections raised by the Learned Examiner under section 2(1)(j), 2(1)(ja) and 8..

(i) The applicant at the outset wish to briefly summarize the crux of the invention as disclosed in the patent specification.

The patent application number 339/MUMNP/2006 is directed to a pharmaceutical composition which comprises a **solid dispersion** of Ritonavir (or ritonavir and another HIV protease inhibitor) in at least one pharmaceutically acceptable **water soluble polymer** and at least one **pharmaceutically acceptable surfactant**.

We wish to bring to the Hon'ble Controller's attention the meaning of the aforementioned underlined expressions which are very fundamental to the interpretation and understanding the scope of the present application.

It is submitted that on page 2 of the international application, **solid dispersion** has been defined as a system in a solid state (as opposed to a **liquid** or **gaseous** state) comprising at least two components, wherein one component is dispersed evenly

throughout the other component or components. For example, the active ingredient or combination of active ingredients is dispersed in a matrix comprised of the pharmaceutically acceptable water-soluble polymer(s) and pharmaceutically acceptable surfactant(s). The term "solid dispersion" encompasses systems having small particles, typically of less than 1 mm in diameter, of one phase dispersed in another phase. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase (as defined in thermodynamics), such a solid dispersion will be called a "solid solution" or a "glassy solution". A glassy solution is a homogeneous, glassy system in which a solute is dissolved in a glassy solvent. Glassy solutions and solid solutions of HIV protease inhibitors are preferred physical systems. These systems do not contain any significant amount of active ingredients in their crystalline or microcrystalline state, as evidenced by thermal analysis (DSC) or X-ray diffraction analysis (WAXS).

"Ritonavir" is a class IV compound under the Bio Pharmaceutics Classification system. Class IV compounds have low aqueous solubility and low membrane permeability and therefore have poor bioavailability and are not well absorbed by gastro intestinal mucosa. For this reason Class IV compounds are the most difficult of compounds to be formulated into a solid form so as to provide adequate solubility and acceptable permeability to achieve satisfactory bioavailability. See paragraphs 3 - 7 of Breitenbach's Declaration.

Ritonavir is also practically insoluble in water, and traditionally mixtures of Ritonavir, a water soluble polymer, a surfactant, and other excipients do not significantly improve the solubility of Ritonavir. See paragraphs 9 - 10 of Breitenbach's Declaration. See also page 1 of Zhu et al. (cited as Exhibit 7 by the Opponent).

Another HIV protease inhibitor, for instance lopinavir, can be co-formulated with ritonavir in a solid dispersion of the present invention. Ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir. See page 1 of the U.S. FDA Label (**Annexure 1**).

From page 8, line 10, to page 9, line 23, the patent specification defines the nature of the water soluble polymer that are used in formulating solid dosage form of Ritonavir and/ or other HIV protease inhibitor according to the present invention.

It is submitted that for the present invention, the said formulation includes at least one water soluble polymer which has a transition temperature (T_g) of at least 50°C so as to make the formulation sufficiently temperature stable.

The term “**pharmaceutically acceptable surfactant**” has also been defined on page 6 of the patent specification as being a non-ionic surfactant and preferably having hydrophilic lipophilic balance (HLB) value of from about 4 to about 10.

We wish to further bring to the attention of the Hon’ble Controller, page 6 lines 1 to 9 of the patent specification that provides the technological advantage of the present invention over the existing formulation. It is submitted that the compositions according to the present invention are characterized by excellent stability, in particular, high resistance against recrystallization or decomposition of the active ingredients. **These characteristics directly manifest so as to enhance the bioavailability and therapeutic efficacy of the product**

(ii) Without prejudice, the Applicant reserves the right to provide further evidence and amendment to the specification during the prosecution of the application either under Section 25 of the Indian Patents Act or Section 14 of the Indian Patents Act.

For the purpose of these proceedings, the Applicant will now address the grounds relied upon by the opponent. **The applicants will now deal with the first ground of opposition i.e. Not patentable as under section [25(1)(f)] and 3(d) of the act.**

10-11. The opponent in this paragraph of the written statement has simply reproduced the section that it has relied upon from the Indian Patents Act and the DRAFT manual of patent practice and procedure of the Indian patent office. on the IPO website in and around 2005. It is submitted that it is well established principle that no administrative order or guidelines can have an overriding effect on statutory provisions. Moreover, it is further submitted that the rules that have been relied upon by the opponents are in the DRAFT form and therefore have no bearing whatsoever on the present proceedings

The approach which the opponent seems to have relied upon in paragraph 11 of the written statement is vehemently denied in as much as that any application for patent is to first be assessed under Sections 12 and 13 of the Indian Patents Act as to whether they constitute an invention within the meaning of the Act i.e. section 2(1)(j) and in furtherance thereof, the examiner is required to review the application as to determine whether the claimed invention is novel and inventive over the prior art document. Only once the examiner has assessed the novelty and inventive step of the invention with respect to prior art documents, does he proceed to the other provisions of the Act including Section 3.

12. The allegations of the opponent that the disclosure of ritonavir and lopinavir formulation in application number WO 00/74677, **Exhibit 3**, makes the current invention unpatentable under section 3(d) are denied.

At the outset it is submitted that section 3(d) of the Indian Patents Act does not apply to the present application as the pharmaceutical composition comprising of HIV Protease Inhibitor ritonavir, water soluble polymer and surfactant is a **novel composition** and has not been disclosed in any prior art document. Therefore the applicant submits that the ground of section 3(d) taken by the opponent ought to be set aside.

For the purpose of establishing that section 3(d) does not apply to the present application we would like to bring to the Hon'ble Controller's attention that section 3(d) will be attracted only in the following situations:

- (a) where the invention relates to a mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance; or
- (b) mere discovery of any new property; or
- (c) new use of a known substance; or
- (d) mere use of the known process machine apparatus unless such known process results in a new product or employs at least one new reactant.

In this regard it is stressed that the explanation to this section only aids interpretation of the operative part of section 3(d). The opponent seems to have stressed upon the expression "combinations" appearing in the explanation of section 3(d).

The present application is directed to a novel pharmaceutical composition, which includes ritonavir (or ritonavir and another HIV protease inhibitor) along with a water-soluble polymer and a non-toxic surfactant. There is no document which suggests that this combination is a known combination and therefore we are at the outset not required to establish efficacy of the said composition. It is further submitted that as identified above, the invention according to the present application does not fall under any one of the four categories of Section 3(d) identified above.

In view of our submission the opponent's ground under section 25(1)(f) may be dismissed.

However for the purpose of the present proceedings and without prejudice, the applicant denies the allegations made by the opponent that the current invention is not patentable under section 3(d) in view of WO 00/74677 ('677) (**Exhibit 3**).

It is submitted that '677 describes an improved pharmaceutical composition comprising one or more HIV protease inhibiting compounds having improved dissolution properties in a mixture of fatty acid, ethanol and water and optionally a pharmaceutically acceptable surfactant.

In this regard, we submit that the final formulation according to the '677 is a solution enclosed in a soft elastic gelatin capsule (SGC) or a hard gelatin capsule. This formulation is prone to chemical degradation when the drug product is not stored under refrigerated conditions. The loss of ritonavir therefore by chemical degradation under improper storage conditions can impact product efficacy and the increase in degradation products impact the product safety.

It is further submitted that SGC product stored under controlled room temperature conditions for longer duration fail to establish product specifications

The applicant also wishes to rely on **Exhibit 6 (Annexure 2)** filed by the opponent namely the article on "*Melt Extrusion Can Bring New Benefits to HIV Therapy*" by Jorg Breitenbach (attached as **Annexure 2**) who is also the co-inventor in respect of this application. This document clearly establishes and states that **"there are several problems associated with soft gel capsules. One of them is that chemical instability can arise between the drug, the vehicle and the capsule shell resulting in physical as well as chemical change. Sometimes the active ingredients can crystallize out of solution, thereby reducing bio-availability"**.

The Applicant further relies upon page 63 of the said exhibit which further establishes that SGC requires refrigerated storage and should be taken with food in order to optimize the bio availability of Lopinavir. The composition according to the present application therefore has acceptable oral bioavailability and does not require refrigeration or need to be taken with food.

Though ritonavir and lopinavir were already known and a pharmaceutical formulation comprising ritonavir and lopinavir has been disclosed in WO 00/74677, it is stressed that the present application does not claim ritonavir or lopinavir. Nor does it claim a combination of ritonavir and lopinavir. Instead, the present application claims a composition, which comprises a solid dispersion of ritonavir in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant. In contrast, the formulation of WO 00/74677 includes a **solution**, which comprises an HIV protease inhibitor, a pharmaceutically acceptable organic solvent and water. The physical forms of the composition of the present application and the formulation of WO 00/74677 are

fundamentally different (solid vs. liquid-based). The formulations described in '339 and '677 are commercially manufactured under the trade name of Kaletra. Whereas '339 describes the Kaletra tablet, '677 describes the Kaletra Soft Gel Capsules (SGC).

It is therefore established that the composition of the present application and the formulation described in WO 00/74677 ('677) are different "substances." They also differ significantly in properties with regard to efficacy when compared under fasting and/ or non-refrigerated storage conditions.

It is further submitted that as established above, the two formulation according to '677 and the present invention are different forms i.e solid versus liquid based, their properties will be significantly different with respect to one another, especially with regard to efficacy when compared under a variety of administration and storage conditions. First, the bioavailability and anticipated effectiveness of the formulation of WO 00/74677, but not the composition of the present application, can be significantly affected by food. Ibid paragraphs 6-8 and 10-11 of Chiu's Declaration. Second, ritonavir is less stable in a soft gel capsule formulation of WO 00/74677 than in a solid dispersion of the present application. As indicated in ***"Kaletra SGC- tablet stability Comparison"*** (**Annexure 3**), on page 1, the performance of Lopinavir is highly dependent on the proper amount and performance of the pharmacokinetic enhancer ingredient, Ritonavir. Ritonavir in the Kaletra SGC is prone to chemical degradation when the drug product is not stored under refrigerated conditions. Loss of ritonavir can impact product efficacy; increased degradation products can impact product safety. Therefore, the SGC formulation can be significantly less potent than the Tablet formulation after storage under non-refrigerated conditions. Ibid paragraphs 5-8 of Morris's Declaration. The regression analysis data supporting Morris's Declaration is annexed (**Annexure 4**)

Annexure 3 through comparative tables on pages 4-6, further exemplifies the following:

- Kaletra SGC product stored under controlled room temperature conditions (25°C) for longer durations will fail the established product specifications. For example, the ritonavir content (potency) and the level of ritonavir degradation products will fail specifications between 6-18 months.
- At higher temperatures, such as 30°C, the Kaletra SGC product will fail the established product specifications more rapidly. For example, the ritonavir content (potency) and the level of ritonavir degradation products will fail specifications in ~2-6 months.

- Exposure of the Kaletra SGC product to temperatures of 40°C or higher for extended periods can lead to deformation or damage to the gelatin capsule, potentially resulting in rupture and leakage of the liquid fill. Therefore, the Kaletra SGC is not a viable product when storage conditions are greater than or equal to 40°C.
- The Kaletra Tablet has no special storage requirements.
- The Kaletra Tablet shows no significant change in ritonavir content or levels of ritonavir degradation products when stored at 25-30°C for at least 36 months, 40°C for at least 6 months, and 50°C for at least 3 months.

To summarize, LPV and RTV potency is always higher in Kaletra tablet than in SGC after several months of storage.

To further support aforementioned contentions the Applicant relies on the following documents:

- ***Jon Lewis “Solid Solutions for Insoluble Substances”, Drug Delivery Report Spring/Summer 2006 (Annexure 5)*** which states that “The first marketed Kaletra product was a soft-gel capsule formulation, each capsule containing 133mg lopinavir/ 33mg ritonavir, with an adult regimen of 6 capsules per day. The new Kaletra tablet made using Abbott’s Meltrex Technology, contain 200mg lopinavir/50 mg ritonavir per tablet in a solid solution with a resulting adult regimen of only four tablets per day. The convenience benefits for patients from this new formulation also include, not only the reduction in the daily ‘pill-burden’ but, in addition and very importantly the tablets can be taken with or without food and they do not need refrigeration before or after dispensing”.

Annexure 1, further supports our submissions that states that:

“Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg KALETRA tablets are similar to three 133.3/33.3 mg KALETRA capsules under fed conditions with less pharmacokinetic variability.”

It is therefore prayed that this ground of the opponents be dismissed

- 13 The contents of paragraph 13 of the written statement are denied that '339 is merely the same substance as the previously known form ('677) and that the application fails to meet the efficacy requirement as no relevant evidence is submitted. There is no requirement under the Indian Patent Act and rules to make a claim in a patent application to show efficacy. The opponent has failed to appreciate that under the Act and rules, the applicant can satisfy the controller on any issue irrespective of its nature be it novelty or obviousness by way of explanation and submissions made in response to office actions or by way of affidavits.

Without prejudice, should the Honorable controller feel necessary in order to establish any grounds under the Indian Patent Act and rules we are willing to amend the specification accordingly.

It is further submitted that the composition of the present application and the formulation of WO 00/74677 are different "substances." The water-soluble polymer(s), surfactant(s) and ritonavir of the composition claimed in the present application are each functionally required for the solid dosage form vis a vis composition according to the present invention to work properly. The HIV, protease inhibitor, the organic solvent and water are also functionally required for the formulation of WO 00/74677 to work properly.

The formulation of WO 00/74677 does not include any "solid dispersion" or "pharmaceutically acceptable water-soluble polymer", and the composition of the present application does not include any liquid solution or organic solvent. In addition, the physical forms of the composition of the present application and the formulation of WO 00/74677 are fundamentally different (solid vs. liquid-based). Accordingly, the composition of the present application and the formulation of WO 00/74677 are different "substances," and should not be comparable under section 3(d).

Furthermore, the composition of the present application is not a "combination of known substances" under section 3(d). Instead, the composition of the present application is a new substance because ritonavir, polymer and surfactant in the composition interact with each other in a novel and inventive way, thereby creating a new material that is entirely different from the mere mechanical mixture of the individual components. Section 3(d) does not prohibit patentability of novel and inventive compound which has a useful therapeutic indication (e.g., anti-HIV). However, any new, patentable anti-HIV compound is a mere "combination of known substances" in that any such compound is a combination of known atoms such as H, C, N, S, or O. However, section 3(d) does not require that a new, patentable anti-HIV compound have enhanced anti-HIV activities as

compared to all known anti-HIV drugs. This is because if all the known atoms in a new compound are functionally interrelated in a novel and inventive way, the new compound should be patentable regardless of whether it has improved efficacy compared to other anti-HIV compounds. Likewise, a composition of the present invention is patentable because its *components (e.g., ritonavir, water-soluble polymer(s) and surfactant(s)) are functionally interrelated in a novel and inventive way. Because of these functional interrelations, ritonavir in the composition of the present invention has significantly improved bioavailability , the fact being highlighted in examples 2-5 and 7 of the present application. Therefore, the composition of the present invention is a new patentable substance and not a mere “combination of known substances” under section 3(d).*

Even assuming, arguendo, that the composition of the present invention is a “combination of known substances” (e.g., a combination of ritonavir, surfactant(s) and water-soluble polymer(s)), it differs significantly in efficacy as compared to a simple mechanical mixture of ritonavir, surfactant(s) and water-soluble polymer(s). As indicated in paragraph 9 – 10 of Jorg Breitenbach’s Declaration, ritonavir is practically insoluble in water. A simple mechanical mixture of ritonavir with surfactant(s) and polymer(s) does not significantly improve ritonavir’s solubility. As a result, ritonavir in such a mechanical mixture would not be bioavailable and therefore would not be therapeutically effective. **Exhibit 7** of the opponent, Zhu *et al.* (“New Tablet Formulation of Lopinavir/Ritonavir is Bioequivalent to the Capsule at a Dose of 800/200 mg,” presented at 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington DC (2005)), on page 1, also states that unformulated solid Lopinavir/ritonavir “fails to provide bioavailability (<5%),” and “[i]ncorporation of surfactants, acids or other wetting agents with traditional technologies failed to provide adequate bioavailability for solid formulations.”

Being different substances, the functional relationship and interactions between each component in the composition of the present application are entirely different from those in the formulation of ‘677 (e.g., one being interactions in solid phase and the other being interactions in liquid phase), which lead to different properties with regard to efficacy.

It is therefore prayed that the pre-grant opposition be dismissed.

14. The contents of this paragraph are denied. It is humbly submitted that section 3(d) suggests that a new form (different size, polymorph etc of a known substance) that results in an **enhancement of the known efficacy** is patentable. The explanation to the said section **only aids** in the

interpretation of the operative part and states that the enhancement of the known efficacy should be a result of a significant difference in **properties** with regard to efficacy.

Section 3(d) is reproduced herein below: "The following are not inventions within the meaning of this 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 or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation: 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***"

It is clear from the said section and its explanation that the legislative intent of Section 3(d) was to facilitate and protect incremental innovations and not stifle further developments and advancements in this field.

Further, Section 3(d) does not require a **significant improvement in efficacy** to make an invention qualify for a patent. As can be interpreted from the explanation section 3(d) requires a **significant improvement in properties** to result in a more efficacious product. The efficacy need not be quantified to determine whether the product is efficacious because it is not possible to have a standard numerical value for efficacy for all pharmaceutical products. The present invention and the invention claimed in '677 are synergistic combinations of different elements, which result in products possessing significantly different properties. As submitted above, as the two formulation according to '677 and the present invention are different forms i.e solid versus liquid based, their properties will be significantly different with respect to one another, especially with regard to efficacy when compared under a variety of administration and storage conditions. The significantly improved properties of the product claimed in the present invention result in greater potency of the product under different administration and storage conditions as compared to the product claimed in '677. Moreover, without prejudice, for the purpose of Section 3(d), it is submitted without admitting that the two formulations ('677 and present invention) have different properties and if at all efficacy of two

products have to be compared, it has to be compared under same parameters and standards(conditions)

The applicant strongly believes that the opponent has narrowly interpreted the term 'efficacy' so as to subserve its own interests. The statute does not discriminate between inventions belonging to the pharmaceutical and non-pharmaceutical sectors. Nowhere does the Act define the term efficacy to mean only pharmacological and therapeutic efficacy. The opponents have failed to understand and appreciate the ambit of Section 3(d). Section 3(d) includes chemical compounds, intermediates for pharmaceutical products, agro-chemicals, food based chemicals etc, all of which cannot imaginably be required to establish therapeutic efficacy only so as to obtain a patent. Even otherwise, in respect of pharmaceutical products, efficacy can include **therapeutic efficacy** and /or non- therapeutic efficacy such as *improved thermodynamic stability, improved processability, solubility characteristics, better patient compliance, and economic efficacy, reduced microbial drug resistance* etc. According to the laws of interpretation, the terms and expressions used in the statute have to be interpreted so as to justify the purported logical conclusion and not with a view to render a provision ineffective and infructuous.

In the case of present invention, improved stability translates into improved efficacy. The solid dosage form of the present invention is significantly more stable than the Soft Gel Capsule and as a result, contains more ritonavir and less ritonavir degradation products after storage under non-refrigerated conditions (e.g., at 30°C, which is a typical temperature in India between March and September). This stability can translate into an improved bioavailability and therapeutic effect, thereby meeting the criteria of efficacy as discussed in the Novartis judgment of the Chennai High Court. See paragraphs 5-8 of Morris's Declaration. Further, the bioavailability and anticipated efficacy of the soft gel capsule is significantly compromised under fasting conditions, while the bioavailability and anticipated efficacy of the solid dosage form is less affected. See paragraphs 6-8 and 10-11 of Chiu's Declaration. The tablet provides consistent exposure to lopinavir and ritonavir regardless of meal conditions which further reduces pharmacokinetic variability compared to the SGC under any meal condition [**New Kaletra tablet PK study**, Reported by Jules Levin, International AIDS Conference (IAS) Rio de Janeiro, Brazil July 24-27, 2005, Figures 5 and 6 (**Annexure 6**)]. Thus, the solid dosage form and the soft gel capsule have significantly different properties with respect to efficacy.

To summarize Kaletra tablets described in '339 have the following benefits over Kaletra SGCs described in '677:

1. reduced pill count
2. room temperature storage
3. lack of significant food effect
4. lower variability of lopinavir levels compared to the soft-gel capsule

It would be without merit to claim that Kaletra tablet does not have improved efficacy as compared to SGC.

15. The allegations of the opponent that stability is not the key factor that effects actual therapeutic outcome and that the ability to store at room temperature and lower pill burden or patient compliance do not satisfy the definitions of efficacy are strongly denied. As demonstrated by Morris's Declaration and in our preceding paragraphs along with the annexures, referred to above, the solid dosage form is more potent than the soft gel capsule formulation after non-refrigerated storage. Paragraphs 5 - 8 of Morris's Declaration show that the projected potency of ritonavir in the soft gel capsule formation reduces to about 81% after 6-month storage at 40°C, which temperature is common in India during summer times. In contrast, the potency of ritonavir in the solid dosage form maintains at 97% after 6-month storage at 40°C, and 96% after 3-month storage at 50°C. Similarly, the potency of ritonavir in the soft gel capsule formation reduces to 91% after 6-month storage at 30 °C, and the projected potency of ritonavir reduces to about 81% after 12-month storage, and about 62% after 24-month storage, at 30°C. In comparison, the potency of ritonavir in the solid dosage form maintains at 98% after 12-month storage, and 97% after 24-month storage, at 30°C.

Paragraph 6 of Morris's Declaration also shows that the soft gel capsule formulation fails the established product specifications when stored at 25°C for 6-18 months or at 30°C for 2-6 months. Ritonavir in the soft gel capsule formulation is prone to chemical degradation when stored under non-refrigerated conditions, and the increased degradation products can impact product safety. In comparison, the solid dosage form shows no significant change in ritonavir content or levels of ritonavir degradation products when stored at 25-30°C for at least 36 months. Therefore, the solid dosage forms of the present application and the soft gel capsule formulations of WO 00/74677 exhibit significant difference in ritonavir potency and bioavailability when stored under non-refrigerated conditions. For HIV patients residing in economically challenged or developing countries where refrigerators are not as common in households, the solid dosage form has an apparent advantage over the soft gel capsule formulation. Based on the foregoing, the soft gel capsule formulation described in WO 00/74677 and the solid dosage forms of the present application exhibit different properties with regard to efficacy when compared under a variety of storage conditions (e.g., at 30°C for 12 months or at 40°C for 6

months). To further substantiate the contention of stability of Ritonavir and Lopinavir in Tablets the applicant relies on **Annexure 3**, pages 4-6. Accordingly, section 3(d) should not apply to the present application.

The opponent contends that improved stability of the solid dosage form does not mean improved efficacy. However, as demonstrated above, the solid dosage form is more stable and therefore degrades less when stored under non-refrigerated conditions. As a result, the solid dosage form contains more active ritonavir and is therefore more potent and more bioavailable than the soft gel capsule after non-refrigerated storage. Accordingly, improved stability does translate into improved efficacy in this case, when the formulations are compared under the same non-refrigerated storage conditions. Thus, the solid dosage form and the soft gel capsule have significantly different properties with respect to efficacy.

16. The contents of this paragraph are denied in entirety. In this regard the applicant submits that the opponent has failed to appreciate the fact that the similarity in bioavailability between the present invention and '677 is restricted to the administration of the respective dosage forms under fed conditions. This fact is exemplified by lines 1-2 on page 2 and lines 1-2 on page 4, of *Zhu et al (cited as Exhibit 7* by the opponent).

Paragraph 8 of Chiu's Declaration also demonstrates that under fasting conditions, lopinavir AUC and C_{max} of the tablets formulation are 62 and 46% higher, respectively, than lopinavir AUC and C_{max} of the soft gel capsule formulation. This is further supported by the results of the study M03-616 on page 8 of the European Medical Agency (EMA) publication entitled 'Scientific Discussion', London, 27 April 2006, (**Annexure 7**).

The bioavailability and thus the anticipated efficacy of the formulation of WO 00/74677, but not the formulation of the present application, can be significantly affected by whether the formulation is administered under fasting or fed conditions. Paragraph 6 of Chiu's Declaration indicates that relative to fasting, administration of a soft gel capsule formulation under moderate-fat meal conditions increases lopinavir AUC and C_{max} by 48 and 23%, respectively. The declaration is supported by the FDA label entitled "**KALETRA®** (lopinavir/ritonavir) capsules (lopinavir/ritonavir) oral solution" (**Annexure 8**) which on page 7 under the subheading "Effects of food on oral absorption"

As a consequence, the soft gel capsule formulation is recommended to be taken with food in order to enhance bioavailability and minimize pharmacokinetic variability.

In comparison, Zhu *et al.* (**Exhibit 7**) describes that a solid dispersion of ritonavir and lopinavir “provided more consistent LPV [lopinavir] and RTV [ritonavir] exposure across meal conditions (fasting, moderate fat meal, high fat meal), with reduced pharmacokinetic variability compared to the SGC [soft gel capsule formulation].” This fact is further substantiated by **Annexure 1**, which on page 8 states that:

“Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg KALETRA tablets are similar to three 133.3/33.3 mg KALETRA capsules under fed conditions with less pharmacokinetic variability”

“No clinically significant changes in C_{max} and AUC were observed following administration of Kaletra tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of KALETRA tablets with a moderate fat meal (500 – 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 26.9% and 17.6%, respectively. Relative to fasting, administration of KALETRA tablets with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC by 18.9%, but not C_{max}. Therefore, Kaletra tablets may be taken with or without food.”

In addition, paragraph 7 of Chiu’s Declaration shows that fasting and fed conditions have significantly less effect on the bioavailability and, therefore, the anticipated efficacy of lopinavir in a solid dosage form of the present application. This is further supported by **Annexure 7**, which on page 7 states that:

“a supra-bioavailability of the tablet formulation as compared to the currently marketed formulation[SGC] was consistently shown ”.

Annexure 7, on page 10 further states that:

“Based on the results of this study M03-616 it appears that the food influence is much more noticeable for the capsule (» 40% increase of the exposure) than for the tablet formulation (» 20% increase of the exposure). This justifies a capsule intake “with food only”, whereas the to-be-marketed tablet formulation could be administered “with or without food”.

“Moreover, when considering the relative bioavailability between the tablet and capsule formulation under fast and fed conditions

:

- Under fed conditions (C/A) a supra-bioavailability of the tablet formulation is observed as compared to the capsule formulation.

- This supra-bioavailability is even more noticeable under fasting (D/B) conditions (likely in relation with the sub-optimal conditions of drug intake for the capsule formulation which is only to be administered with food).”

As a result, the solid dosage form can be taken with or without food, without significantly affecting bioavailability and efficacy. This feature represents a significant difference with regard to efficacy between the formulation of the present application and the soft gel capsule formulation of WO 00/74677.

Further, **Exhibit 6** relied upon by the opponent itself states that the new tablet formulation can be stored at room temperature and can be taken without regard to food. No such advantages are known for '677.

In paragraph 16, the opponent urges that the compositions of the present application not be compared to “another melted formulation as shown in the Examples of the specification on 15-19” but be compared “against the other well-known, widely prescribed form of the known combination Lopinavir/Ritonavir ('677).” However, as discussed above, the present application does not claim a “combination of lopinavir and ritonavir.” Instead, the present application claims a composition comprising **a solid dispersion** of ritonavir in at least one pharmaceutically acceptable water-soluble polymer and at least one pharmaceutically acceptable surfactant. These ingredients are functionally interrelated in the claimed composition, making the composition a different “substance” than the formulations described in WO 00/74677. As is apparent from **Annexure 3**, the performance of Lopinavir is highly dependent on the proper amount and performance of the pharmacokinetic enhancer ingredient, Ritonavir. Loss of ritonavir can impact product efficacy. The inter-relation of elements of '677 formulation is such that Ritonavir is prone to chemical degradation when the drug product is not stored under refrigerated conditions. Also, the bioavailability of active ingredients in SGC is affected by food intake. On the other hand, the functional inter-relation of the elements of the '339 composition results in a product that is not affected by storage conditions and food intake. Therefore, the formulations of WO 00/74677 should not be used as a reference for the purpose of section 3(d) comparison. Even assuming, arguendo, section 3(d) applies, the proper reference should be a mechanical mixture of ritonavir, the water-soluble polymer(s) and the surfactant(s). As indicated above, the composition of the present application has significantly improved bioavailability and efficacy as compared to the mere mechanical mixture of the individual ingredients. See also paragraphs 9-10 of *Breitenbach's Declaration, and page 1 of Zhu et al. (cited by the opponent as Exhibit 7)*.

17. The content of this paragraph is vehemently denied. In paragraph 17, the opponent contends that Zhu *et al.* (**Exhibit 7**) showed that the tablet form is bioequivalent to the soft gel capsule. However, the comparison in Zhu *et al.* was performed under moderate-fat meal conditions, without considering other food conditions (e.g., fasting) or non-refrigerated storage conditions (e.g., at 25-30°C, which is common in developing countries). As demonstrated above, the soft gel capsule and the tablet form are significantly different in bioavailability and efficacy under a wide range of administration and storage conditions (e.g., under fasting conditions or after 6-month storage at 40°C or 12-month storage at 30°C). In fact, Zhu *et al.* found that the tablet form “provided more consistent LPV [lopinavir] and RTV [ritonavir] exposure across meal conditions (fasting, moderate fat meal, high fat meal), with reduced pharmacokinetic variability compared to the SGC [soft gel capsule formulation].” The opponent’s allegation reflects only one particular comparison under a specific use condition (i.e., under moderate-fat meal and refrigeration), and does not represent all other use conditions (e.g., under fasting or non-refrigerated storage). As demonstrated above, under these other conditions, the tablet and the soft gel capsule have significant differences in bioavailability and efficacy.

18. Taking all of the aforesaid facts in consideration it is without merit to claim that the current invention is the same as or is a derivative of the invention claimed in WO 00/74677. Even assuming, *arguendo*, that the formulation of WO 00/74677 could be used as a reference, for the reasons set forth above, the composition of the present application is significantly different in properties with respect to efficacy under a variety of conditions (e.g., fasting or after long non-refrigerated storage). Hence the opponents arguments based on section 3(d) are without merit.

The applicants will now deal with the second ground of opposition i.e. Obviousness as under section [25(1)(e)] and 2(1)(j) of the act.

19- 21. The contents of these paragraphs are denied in entirety and merit no reply

22-23 In paragraph 22, the opponent contends that WO 01/34119 (cited as **Exhibit 8** by the opponent) discloses a solid dispersion comprising ritonavir and/or lopinavir in a water-soluble carrier polyethylene glycol (PEG), a crystallization inhibitor polyvinylpyrrolidone (PVP) and surfactants and that it “would have been obvious . . . to select water-soluble polymers . . . like PVP . . . alongside surfactants in order to make poorly water-soluble compounds like Ritonavir and/or Lopinavir have better dissolution with suitable oral bioavailability and stability.” The Applicant submits that WO 01/34119 does not teach or suggest the solid dispersion of the present invention for the following reasons:

- As indicated in paragraphs 24 of Breitenbach's Declaration, the solid dispersion of the present invention employs a water-soluble polymer (e.g., copovidone or PVP) to form an amorphous matrix in which ritonavir and surfactant(s) are distributed. The addition of surfactant(s) to this amorphous matrix significantly improves the bioavailability of ritonavir, which is demonstrable on a comparison between examples 1-7 and to the comparative Example on pages 15-16 of the present application. In contrast, the solid dispersion system of WO 01/34119 employs a crystalline matrix formed by PEG (or other suitable non-amorphous polymers), and ritonavir resides in this crystalline matrix. See paragraph 24 of Breitenbach's Declaration. **In WO 01/34119, PVP functions as a crystallization inhibitor, as opposed to a matrix builder. Therefore, the solid dispersion of the present invention is patently different from that of WO 01/34119. Nor does WO 01/34119 suggest that the crystalline matrix could be replaced with an amorphous matrix.**

- Specifically, WO 01/34119 states that the "benefits of incorporating PVP into the PEG matrix are two fold." See page 11, lines 7-8, of WO 01/34119. WO 01/34119 also states that one "benefit of adding PVP is an increase in amorphous volume of the polymer matrix where drugs reside" and "since polyethylene glycols tend to be highly crystalline, this increase in amorphous volume could be important for fast dissolution." See page 11, lines 11-16, of WO 01/34119.

- Moreover, in all the Examples of WO 01/34119, the PVP over PEG ratio is no more than 20:80, indicating that crystalline PEG, not amorphous PVP, is primarily responsible for the formation of the matrix.

- Therefore, the formulation of WO 01/34119 is crystalline matrix-based, which is fundamentally different from the amorphous matrix-based formulation of the present application. WO 01/34119 neither teaches nor suggests that ritonavir can be stabilized in an amorphous matrix, such as a matrix formed by PVP or another amorphous polymer.

In fact, WO 01/34119 teaches away from the present invention. By the opponent's own admission in paragraph 24, WO 01/34119 "may not specifically disclose that a water-soluble polymer such as PVP could be directly used to form its own matrix without PEG in which poorly water-soluble drugs like Ritonavir and/or Lopinavir can be stably dispersed and suitable bioavailability be maintained."

That WO 01/34119 teaches away from the present invention is supported by the following facts:

- WO 01/34119 actually teaches away from using PVP matrix to stabilize ritonavir. On page 11, lines 7-8, WO 01/34119 states that the “benefit of incorporating PVP into the PEG matrix are two fold,” indicating that using PVP alone would not enjoy the “two fold” benefits.
- WO 01/34119, on page 11, lines 8-10, further explains the “benefit of incorporating PVP into PEG” as follows:
 - Firstly, processing PVP can be difficult due to its hygroscopicity. Secondly, when PVP dissolves a viscous layer at the solid-liquid interface forms. This viscous region can hinder dissolution of the drug.

Accordingly, WO 01/34119 teaches away from using PVP alone because of the above-cited disadvantages. Apparently, these disadvantages had not been resolved at the time WO 01/34119 was filed. See also paragraph 25 of Breitenbach’s Declaration (“One of ordinary skill in the art would consider that these benefits teach against using PVP as the principle carrier to form a drug-supporting matrix for the enhancement of bioavailability”).

- 24-25. The contents of these paragraphs are denied in entirety. In paragraphs 24 and 25, the opponent attempts to combine U.S. Patent No. 4,769,236 (cited as Exhibit 9, hereinafter referred to as ‘236 patent) to remedy the deficiency of WO 01/34119. However, like WO 01/34119, the ‘236 patent does not teach or suggest using a crystallization inhibitor such as PVP to form an amorphous matrix to stabilize ritonavir.
- The ‘236 patent states that “according to the invention the concentration of the inhibiting agent present at the time of spraying is comprised between 1 and 50% with respect to the active principle (weight/weight).” See column 2, lines 3-6. Example 1 of the ‘236 patent uses only 10% of PVP with respect to the weight of the active principle. Example 2 of the ‘236 patent uses no more than 35% of PVP with respect to the weight of the active principle.
 - Claim 1 of the ‘236 patent also prescribes the use of “a stabilizing and crystal-formation-inhibiting amount of between about 1 to 50% w/w with respect to the active principle of polyalkyleneglycol-polyvinylpyrrolidone.”
 - Because the amount of the crystallization inhibitor used in the ‘236 patent is less than 50% of the amount of the active principle, the crystallization inhibitor cannot form a matrix in which the active principle is dispersed and stabilized. Accordingly, like W01/34119, the formulation of the ‘236 patent is fundamentally different from the solid dispersion of the present application. See also paragraph 22 of Breitenbach’s Declaration.

Even assuming, arguendo, that the crystallization inhibitor employed in the '236 patent forms an amorphous matrix, the formulation of the '236 patent would not work for ritonavir. The formulation of the '236 patent does not include any surfactant. As demonstrated by the Comparative Example of the present application, ritonavir in such an amorphous matrix (without surfactant) would have poor bioavailability. See paragraph 23 of Breitenbach's Declaration.

Furthermore, as observed in paragraphs 5-7 and 23 of Breitenbach's Declaration, there is no magic formulation that works for all drugs. This is particularly true for ritonavir, a Class IV compound under the Biopharmaceutics Classification System. Class IV compounds have low aqueous solubility and low membrane permeability. Class IV compounds are among the most difficult to be formulated into solid dosage forms, partly because membrane permeability, as compared to solubility, is less likely to be improved by formulation. See paragraphs 3-7 of Breitenbach's Declaration. To achieve acceptable bioavailability, a Class IV compound must be formulated to provide both adequate solubility and acceptable permeability, and improvement in dissolution does not correlate with improvement in bioavailability. A person skilled in the art cannot reasonably predict, without actual testing, if a given formulation would work for a Class IV compound. There is no general formulation for Class IV compounds, and extensive research must be conducted for each Class IV compound in order to identify formulations that can provide adequate bioavailability. Specifically, considerable technical challenges must be resolved in order to formulate a Class IV compound, such as ritonavir, into a solid dosage form. See paragraphs 6 and 12 of Breitenbach's Declaration.

The traditional trial-and-error approach, though often time-consuming and labor-intensive, does not guarantee the identification of a suitable formulation for a Class IV compound. See paragraph 6 of Breitenbach's Declaration. It was not expected that the solid dispersion of the present invention would work for ritonavir, and the first attempts to use solid dispersion technologies to improve ritonavir bioavailability had failed, as exemplified in the Comparative Example of the present application. See paragraphs 9-14 of Breitenbach's Declaration. The solid dosage formulation of the present invention was the result of years of intense research. See paragraphs 12-14 of Breitenbach's Declaration.

- 26- 27. The contents of these paragraphs are denied in entirety. In paragraphs 26-27, the opponent seems to argue that because the methods of the '236 patent worked for hydroflumethiazide and dipyridamole, the methods would also work for all other poorly water-soluble compounds including ritonavir and lopinavir. These arguments / statement of the opponent are without any merit. However, as discussed above, the formulation described in the '236 patent is entirely different from that of the present application. In addition, the formulation of the '236

patent does not include any surfactant and, therefore, would not likely work for ritonavir, as demonstrated by the Comparative Example of the present application.

As stated earlier and appreciated by one of ordinary skill in the art, there is no magic formulation that works for all compounds, particularly for Class IV compounds such as ritonavir. See paragraph 23 of Breitenbach's Declaration. As noted above, a person skilled in the art cannot reasonably predict, without actually testing, if a given formulation would work for a Class IV compound. See paragraphs 5-6 of Breitenbach's Declaration. Hydroflumethiazide and dipyridamole are structurally different from ritonavir. Therefore, without testing, one of ordinary skill in the art could not predict with any certainty if the formulation of '236 would work for ritonavir. See paragraphs 5-7 and 23 of Breitenbach's Declaration. In fact, Breitenbach ("Melt Extrusion Can Bring New Benefits to HIV Therapy - The Example of Kaletra® Tablets," Am. J. of Drug Delivery, 4(2), 61-64 (2006)), which is cited by the opponent as **Exhibit 6**, states that "[n]early 10 years of research and equipment modification were required to successfully incorporate the active ingredients of Kaletra® into a tablet with satisfactory bioavailability and storage requirements." See page 62, right column, of **Exhibit 6**. **Exhibit 6** in the Abstract on page 61 also states that "[t]he incorporation of poorly soluble drugs into convenient oral dosage forms is one of the biggest challenges encountered in drug formulation" and "[a]pplication of melt extrusion to the manufacturing of tablets is relatively new, complex, and is technically challenging." . Therefore, extensive and time-consuming research, as well as substantial inventive steps, had been performed to develop a solid dispersion of the present invention. . See paragraphs 9-16 of Breitenbach's Declaration.

Specifically, prior to the present invention, solid formulations of ritonavir had showed poor bioavailability. The first attempts to use solid dispersion technologies to improve ritonavir bioavailability failed, as shown in the Comparative Example of the present application. Because ritonavir is a Class IV compound which is both poorly soluble and poorly permeable, and the solid dispersion technology was originally designed to improve solubility and/or dissolution rates but not membrane permeability according to the Noyes-Whitney equation, one of ordinary skill in the art would not have expected that further modifications of the solid dispersion technology would lead to improved bioavailability of ritonavir. See paragraph 14 of Breitenbach's Declaration.

It was totally unexpected that surfactants, such as surfactants with HLB values of from about 4 to about 10, can significantly improve the bioavailability of ritonavir in an amorphous polymer matrix. See paragraph 15 of Breitenbach's Declaration. Those skilled in the art would not have any reasonable expectation

of success that the addition of surfactants to an amorphous polymer matrix could improve the bioavailability of ritonavir or another Class IV compound. See paragraph 16 of Breitenbach's Declaration. Prior to the present invention, those skilled in the art did not know, and could not predict, what effect a surfactant might have on the bioavailability of a Class IV compound in an *amorphous polymer matrix*.

Accordingly, the opponent's assertion that "it would have been obvious to try PVP, with more than a reasonable expectation of success, for other poorly soluble compounds like Ritonavir/Lopinavir" is baseless or, at best, the result of the use of impressive hindsight, not to mention that the formulation of the '236 patent is not likely to work for ritonavir due to lack of surfactants. See paragraph 22-23 of Breitenbach's Declaration.

28. The contents of this paragraph that PVP could be used to form its own matrix are made all the more obvious by '119 which identify the utility of PVP in providing a stable, non-crystalline (amorphous) matrix for drug delivery are denied. The cited paragraphs and figures (5-8) do not even hint that PVP can be used to form its own matrix. In contrast, WO 01/34119 specifically states on page 11, lines 3-5, that "PVP PF 17 is used within the PEG matrix to inhibit the crystallization of the drug of interest." Figures 5-8 also describe matrices formed by either PEG alone, or PEG and PVP in a ratio of 95:5 or 85:15, but not PVP alone.

In paragraph 28, the opponent further alleges that "as could be inferred from '119, a person skilled in the art would know that removing PEG entirely and using PVP alone is a simpler technology to achieve solubility, bioavailability and stability, as it would avoid the possibility that PEG may increase the molecular mobility and result in crystallization of Lopinavir/Ritonavir." This inference of the opponent is vehemently denied. The applicant submits that the inference drawn by the opponent is misleading as '119 does not even hint that removal of PEG entirely and using PVP alone is a simpler technology. On the contrary '119 teaches away from the use of PVP alone because of several disadvantages that had not been resolved at the time WO 01/34119 was filed. In particular, WO 01/34119 states on page 11, lines 7-10:

The benefit of incorporating PVP into the PEG matrix are two fold. Firstly, **processing PVP can be difficult** due to its hygroscopicity. Secondly, **when PVP dissolves a viscous layer at the solid-liquid interface forms. This viscous region can hinder dissolution of the drug.**

Thus it would be illogical to state that it would have been obvious for a person skilled in the art to use what WO 01/34119 teaches away from.

Moreover, as discussed, WO 01/34119 describes a crystalline matrix-based formulation, while the formulation of the present application is amorphous matrix-based. Any attempt to transform a crystalline matrix-based formulation to an amorphous matrix-based formulation would require a fundamental change of the formulation, and one of ordinary skill in the art would not be able to predict if, after such a fundamental change, the modified formulation would work like the original one. See paragraphs 24-25 of Breitenbach's Declaration.

29. The contents of this paragraph are denied in entirety. In paragraphs 29-37, the opponent continues to attempt to use impermissible hindsight to reconstruct the present invention by selectively using or combining references. However, as discussed below, all the references cited by the opponent, either alone or in combination, do not teach or suggest the formulation of the present application. See paragraphs 17-20 and 27-33 of Breitenbach's Declaration

30-31. The contents of these paragraphs are vehemently denied. In paragraphs 30-31, the opponent cites BASF, *ExAct – Excipients and Actives for Pharma*, No. 2, July 1999 (BASF) (**Exhibit 12**), and contends that “it is clear that the use of PVP to form its own amorphous matrix as claimed in ‘339 did not involve any inventive step and was merely the use of existing knowledge and technology.” However, the paragraph cited by the opponent (page 3 under the heading “Complex Formation with soluble PVP”) only describes that complexation with PVP may enhance solubility. It does not teach or suggest that PVP alone can be processed into a matrix for formulation of drugs. In complex formation, PVP forms different complexes with other chemical compounds. Complex formation is different from solid dispersion. See paragraphs 27-28 of Breitenbach's Declaration.

Exhibit 12 cited by the opponent describes that Kollidon can be processed by melt extrusion into a matrix in which drug can be suspended or dissolved. However, **Exhibit 12** does not teach or suggest which types of drugs can be formulated using Kollidon. As discussed above, there is no magic formulation that works for all drugs, particularly Class IV drugs such as ritonavir. See paragraphs 5-7 and 23 of Breitenbach's Declaration. Accordingly, in view of **Exhibit 12**, one of ordinary skill in the art could not predict with any certainty that the bioavailability of ritonavir can be improved by either using Kollidon matrix or PVP complexation. In fact, the Comparative Example of the present application shows that ritonavir in a copovidone matrix (without surfactant) made using melt extrusion does not have the desired bioavailability. Copovidone, also known as Kollidon VA 64, contains 60 wt % N-

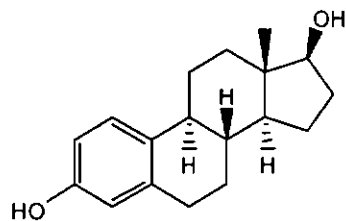
vinylpyrrolidone and 40 wt % vinyl acetate. See page 3 of **Exhibit 12** under the heading “Copolymerization.” In addition, **Exhibit 12** does not teach or suggest using surfactant with PVP or copovidone to improve bioavailability of drugs. As discussed in paragraphs 11-16 of Breitenbach’s Declaration, the effect of surfactant on ritonavir bioavailability in solid dispersions was totally unexpected.

Also as noted above, **Exhibit 6** cited by the opponent states that “[a]pplication of melt extrusion to the manufacturing of tablets is relatively new, complex, and is technically challenging” and that “[n]early 10 years of research and equipment modification were required to successfully incorporate the active ingredients of Kaletra[®] into a tablet with satisfactory bioavailability and storage requirements.” See the Abstract on page 61, and page 62, right column. Therefore, formulating ritonavir in a solid dispersion comprising surfactant(s) and amorphous polymer(s) to improve bioavailability is not at all obvious in light of **Exhibit 12**.

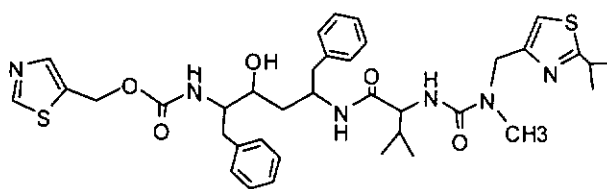
32. The contents of this paragraph that the selection of suitable polymers for ‘339 required no inventive step, but was made predictable given known technologies at that time such as melt extrusion are denied. On page 114, **Exhibit 13** describes a solid dispersion comprising 10% 17-Estradiol, 50% PVP and 40% Geluciree 44/14 has a 30-fold increase in dissolution rate. However, like all other references cited by the opponent, **Exhibit 13** does not suggest that one of ordinary skill in the art would have a reasonable expectation of success that the same formulation would work for ritonavir. As noted, there is no magic formulation that works for all drugs, particularly Class IV drugs such as ritonavir. See paragraphs 5-7 and 23 of Breitenbach’s Declaration. Indeed, **Exhibit 6** asserts that “[a]pplication of melt extrusion to the manufacturing of tablets is relatively new, complex, and is technically challenging” and that “[t]o date, only four drugs have been successfully manufactured using melt extrusion technology.” and “[**K**]aletra containing the anti- HIV protease inhibitors Lopinavir and Ritonavir, is **the first co-formulated pharmaceutical compound to be successfully tableted** using a proprietary melt extrusion process.” If the opponent’s contention were correct, it would be astonishing to know that only four drugs had been successfully made using melt extrusion within the period of four years between the publication of **Exhibit 13** (2002) and that of **Exhibit 6** (2006).

Moreover, as appreciated by one of ordinary skill in the art, the fact that a formulation works for one compound does not give rise to any reasonable expectation of success that the same or similar formulation would work for a structurally very different compound. In this case, the structural difference between 17-Estradiol and ritonavir is substantial. Therefore, those skilled in the art would not have any reasonable expectation of success that the 17-Estradiol

formulation described in Exhibit 13 would also work for ritonavir. . See paragraphs 17-20 of Breitenbach's Declaration.



17-Estradiol



Ritonavir

More importantly, 17-Estradiol is a Class II compound under the Biopharmaceutics Classification System, which means that it has low aqueous solubility but high membrane permeability. See paragraphs 19-20 of Breitenbach's Declaration. As observed in paragraph 8 of Breitenbach's Declaration, Class II compounds are often the best candidate for using formulations, such as solid dispersions, to improve solubility and thereby bioavailability. This is because the improvement in solubility of a Class II compound directly correlated with the improvement in its bioavailability. This is in contrast to Class IV compounds such as ritonavir, where improvement in solubility does not necessarily correlate with improvement in bioavailability. See paragraph 4 of Breitenbach's Declaration.

Melt extrusion, as well as other solid dispersion technologies, were originally designed to improve solubility and/or dissolution rates, but not membrane permeability. See paragraph 18 of Breitenbach's Declaration. The effect of solid dispersion formulation on the bioavailability of 17-Estradiol, a Class II compound, is therefore not indicative of whether the same or similar formulation would work for a Class IV compound such as ritonavir. A person skilled in the art would not have any reasonable expectation of success that a formulation which works for a Class II compound would also work for a Class IV compound. See paragraph 20 of Breitenbach's Declaration.

33. The contents of this paragraph are denied in entirety. In paragraph 33, the opponent contends that Serajuddin (cited as **Exhibit 14** by the opponent) and Encyclopedia of pharmaceutical technology (cited as **exhibit 15** by the opponent) describe that PVP and other similar water-soluble polymers can be used as a carrier for solid dispersions. However, like all other cited references, **Exhibit 14** does not teach or suggest that ritonavir, a Class IV compound, can be formulated and stabilized in a matrix made from PVP or other water-soluble polymers. Moreover, as demonstrated in the Comparative Example of the

present application, such a matrix would not work for ritonavir without the addition of surfactants.

Exhibit 14 also recognizes the lack of reasonable expectation of success for applying existing formulations to ritonavir. **Exhibit 14** states at page 1063, right column:

“The bioavailability of ritonavir (Norvir, Abbott), another poorly soluble HIV protease inhibitor (solubility <1 µg/mL at pH >2), was enhanced by formulation as a solid dispersion in a mixture of such surface-active carriers as Gelucire 50/13, polysorbate 80 and polyoxyl 35 castor oil.”

Exhibit 14 further states that:

”the crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abbott) from the market. The crystallization of drug adversely influenced the dissolution of the ritonavir capsule, and the product was switched to a thermodynamically stable solution formulation.”

Exhibit 14 continues at page 1063, right column:

“to ensure that a drug would not crystallize out of solid dispersion at a desired storage temperature, it is important to screen drug solubility in different carriers at such a temperature.”

This statement exemplifies that even if a polymer can be successfully used as a carrier for one particular drug it is not possible for a person skilled in the art to predict that the same polymer would also work for another drug.

Exhibit 14 continues at page 1064, right column:

“Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, as exemplified by the recent withdrawal of ritonavir capsules from the market, so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problems that might not be seen in other types of solid dosage forms. Predictive methods will be necessary for the investigation of any potential crystallization of drugs and its impact on dissolution and bioavailability. Possible drug-carrier interactions must also be investigated.”

Therefore, contrary to the opponent's contention, **Exhibit 14** does not provide any suggestion to one of ordinary skill in the art that ritonavir can be formulated and stabilized in a matrix formed by PVP or another like water-soluble polymer. Instead, **Exhibit 14** merely points to "future research" to resolve the ritonavir formulation issue. See also paragraph 29 of Breitenbach's Declaration.

More importantly, despite the discussion of use of PVP as a carrier in solid dispersions, **Exhibit 14** failed to suggest that PVP based solid dispersion could be used to resolve the ritonavir solid formulation problem. This further demonstrates that the formulation of the present application was not obvious to those skilled in the art.

34. The contents of this paragraph are denied. The opponent relies on Encyclopedia of pharmaceutical technology (**Exhibit 15**) which states that:

*"the bioavailability of hydrophobic drugs can be increased by strategies design to enhance the dissolution rate of the drug. This can be achieved in **many cases** by forming a solid dispersion of the drug in a suitable carrier, often a hydrophilic polymer such as PEG or PVP."*

The applicant submits that **Exhibit 15** does not state that PEG or PVP can be used to enhance the dissolution rate of **all** hydrophobic drugs. Further from paragraph 3, lines 1-4, of **Exhibit 14** cited by the opponent, it can be concluded that even if a polymer can be successfully used as a carrier for one particular drug it is not possible for a person skilled in the art to predict that the same polymer would also work for another drug.

In addition as demonstrated by the Comparative Example of the present application, the PVP-based solid dispersion described in Exhibit 15 does not work for ritonavir. See also paragraphs 30-33 of Breitenbach's Declaration.

Corrigan also describes "three-component" solid dispersions, which contain surfactants, polymers and drugs. All the "three-component" examples described in Corrigan involve the use of PEG as the polymer carrier. As noted, PEG forms a **crystalline matrix**, as opposed to an **amorphous matrix**. Therefore, the "three-component" solid dispersions described in Corrigan are patently distinct from the formulation of the present application. See paragraph 31 of Breitenbach's Declaration.

The examples of formulations quoted under the sub-heading of 'Solid Dispersion Systems' in **Exhibit 15**, mention Griseofulvin and Oxodipine. The applicant submits that **Exhibit 15** does not state that PEG or PVP can be used to enhance the dissolution rate of **all** hydrophobic drugs.

Moreover, the surfactants used in Corrigan were to improve dissolution rates. One of ordinary skill in the art would not have expected that surfactant(s) in an amorphous polymer matrix could provide improved bioavailability to Class IV compounds, such as ritonavir, which are not only poorly soluble but also poorly permeable. See paragraph 32 of Breitenbach's Declaration.

Furthermore, one of ordinary skill in the art would not have selected surfactant-containing solid dispersions for the formulation of drugs. Corrigan observes that "Problems have been reported however as to the physical stability of surfactant containing systems, dissolution rates decreasing over a 12-month period." See page 2649, right column. Therefore, those skilled in the art would have avoided using surfactant-containing solid dispersions as it would impose a stability risk to the product. See paragraph 33 of Breitenbach's Declaration.

35. The allegation of the opponent that one ordinarily skilled in the art would know to use surfactants to improve the solubility of a hydrophobic drug like Ritonavir/Lopinavir based on the Handbook of Pharmaceutical Excipients are denied. Once again, the opponent uses hindsight and the present application as blueprint to argue that the present application is obvious. The Handbook of Pharmaceutical Excipients merely provides a general description of the use of surfactants in pharmaceutical compositions. This reference, as well as any other reference cited by the opponent, does not teach or suggest that the addition of surfactant to an amorphous polymer matrix can significantly improve the bioavailability of ritonavir. As demonstrated in paragraphs 9 - 16 of Breitenbach's Declaration, the effect of surfactant on improving bioavailability of ritonavir in an amorphous polymer matrix was totally unexpected. Those skilled in the art would not have any reasonable expectation of success that the addition of surfactants to an amorphous polymer matrix could improve the bioavailability of ritonavir or another Class IV compound. Prior to the present invention, those skilled in the art did not know, and could not predict, what effect a surfactant might have on the bioavailability of a Class IV compound in an amorphous polymer matrix.

Moreover, the Comparative Example of the present application shows that ritonavir in copovidone matrix has poor bioavailability. Because ritonavir is a Class IV compound which is both poorly soluble and poorly permeable, and solid dispersions were originally designed to improve solubility and/or dissolution rates but not permeability according to the Noyes-Whitney equation, one of ordinary skill in the art would not have expected that further modifications of the original solid dispersion formulation would lead to improved bioavailability of ritonavir. In particular, one of ordinary skill in the art would not have any reasonable expectation of success that addition of surfactant

to the copovidone matrix would improve the bioavailability of ritonavir. See paragraph 14 of Breitenbach's Declaration.

The opponent cites WO 00/74677 ('677) to support his argument that the addition of surfactant is obvious. As explained above, '677 is directed to a formulation where ritonavir is already dissolved in liquid solution. Therefore, the formulation of '677 is fundamentally different from the solid dispersion of the present application, and any surfactant used in '677 is not predictive of whether the same surfactant would improve the bioavailability of ritonavir in solid dispersions. See paragraph 26 of Breitenbach's Declaration.

36. The contents of this paragraph are denied in entirety. In respect to paragraph 36, we have demonstrated above that none of the references cited by the opponent teach or suggest that ritonavir can be stabilized in an amorphous polymer matrix while having acceptable bioavailability. Nor do these references teach or suggest that polymers having suitable Tg values can be used to form matrices to stabilize and provide acceptable bioavailability to ritonavir.

Based on all of the above reasons, the solid dosage forms of the present invention are inventive. As stated in **Exhibit 6** cited by the opponent and paragraphs 12-16 of Breitenbach's Declaration years of research and equipment modification had been required to successfully incorporate the active ingredients of Kaletra including ritonavir into a tablet with satisfactory bioavailability and storage requirements. See page 62, right column, of **Exhibit 6**.

We also observe that the Kaletra tablet formulation has achieved great commercial success. After the launch of Kaletra tablet, generic companies almost immediately copied the product, despite the fact that other Kaletra formulation had existed for at least four years. The failure of the generic companies to come up with a solid dosage form also indicates that the formulation of the present application is not obvious.

37. On the basis of the aforesaid arguments the applicants submit that none of the Exhibits cited by the opponent either alone or on combination with the other suggest or teach the current invention nor do they enable a person skilled in the art to arrive at the current invention. Hence the current invention is novel and inventive.

The applicants will now deal with the third ground of opposition i.e. information under section 8, [25(1)(h)].

- 38- 39. The contents of these paragraphs are denied as the applicants have provided all necessary information relating to Section 8 of the Indian Patents Act to the

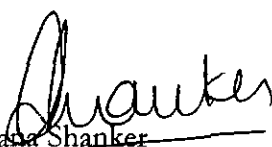
Indian Patent Office. The applicants also will during the course of examination of the application have an opportunity to comply with the Section 8 requirement. This ground of the opponents therefore ought to be dismissed.

In the light of above, we pray the following:

- a) that the patent application no. 339/MUMNP/2006 be granted,
- b) the present pre-grant opposition be dismissed and
- c) costs be awarded to us.

Also, we request the Hon'ble Controller in the interest of natural justice and in view of the powers conferred upon him by Section 80 of the Indian patents Act, grant the applicant a hearing in the above matter preferably along with the opponent.

Dated this day of 8th January, 2008


Archana Shanker

of Anand And Anand, Advocates
Agents for the Applicants